DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE COMMITTEE

OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Wednesday, March, 17, 2004

8:00 a.m.

5630 Fishers Lane
First Floor Conference Room
Rockville, Maryland

PARTICIPANTS

ONCOLOGIC DRUGS ADVISORY COMMITTEE:

Donna Przepiorka, MD., Ph.D., Chair, ODAC
Johanna Clifford, M.S., RN, BSN

Pamela J. Haylock, RN,
Consumer Representative, ODAC

CONSULTANTS (VOTING):

Victor Santana, M.D., Chair
Peter Adamson, M.D.
Alice Ettinger, M.S., RN
Peter Houghton, Ph.D.
Eric Kodish, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Susan Weiner, Ph.D.
Ruth Hoffman, Patient Representative
Barry Anderson, M.D., Ph.D.
Lee J. Helman, M.D.
Malcolm Smith, M.D., Ph.D.
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Kenneth Hastings, Ph.D.

ACTING INDUSTRY REPRESENTATIVE (NON-VOTING):

Antonio Grillo-Lopez, M.D.,

FDA STAFF:

Susan Ellenberg, Ph.D.
Steven Hirschfeld, M.D., Ph.D.
Ramzi Dagher, M.D.
Richard Pazdur, M.D.
Patricia Keegan, M.D.
Pat Dinndorf, M.D.
Grant Williams, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. SANTANA: Good morning to everyone. I know Dr. Kodish is on the line so good morning to you too, Eric. I hope you can hear us well.

DR. KODISH: Good morning, Victor.

DR. SANTANA: This is a meeting of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee and we are here today to advise the agency on two issues. In the morning we will deal with the issue of safety monitoring in clinical studies enrolling pediatric oncology patients. Then, in the afternoon we will address issues related to the use of nonclinical data to complement clinical data for proposed pediatric oncology studies. So, we have quite a busy agenda and I think we will go ahead and get started with the introductions, and I am feeling so sorry for Dr. Anderson who is sitting all by himself over there, but we will go ahead and get started with him and then move around.

Introductions

DR. ANDERSON: Barry Anderson, from NCI CTEP.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez,

Neoplastic and Autoimmune Diseases Disorders Research Institute.

DR. WEINER: I am Susan Weiner, from The Children's Cause, a patient advocate.

MS. HOFFMAN: Ruth Hoffman, patient advocate.

DR. PRZEPIORKA: Donna Przepiorka, University of Tennessee, Memphis.

MS. CLIFFORD: Johanna Clifford, executive secretary to this meeting.

DR. SANTANA: Victor Santana, pediatric oncologist at St. Jude Children's Research Hospital, Memphis, Tennessee.

DR. REYNOLDS: Dr. Reynolds, Children's Hospital of Los Angeles.

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

DR. PAZDUR: This is Susan Ellenberg, who has laryngitis. She is a statistician. I am Richard Pazdur.

DR. HIRSCHFELD: Steven Hirschfeld, FDA.

DR. DINNDORF: Patricia Dinndorf, FDA.

DR. DAGHER: Ramzi Dagher, FDA.

DR. SANTANA: Eric, will you go ahead and

announce your name and affiliation for the record?

DR. KODISH: I am Eric Kodish, from Cleveland, Ohio, Rainbow Babies & Children's Hospital.

DR. SANTANA: Thank you, Eric. With that, we will go ahead and have Ms. Clifford read us the conflict of interest statement.

Conflict of Interest Statement

MS. CLIFFORD: Thank you. The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand. To determine if any conflict of interest existed, the agency has

reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

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

Because general topics impact so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member and consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Antonio Grillo-Lopez is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and

Autoimmune Diseases Research.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

DR. SANTANA: Thanks, Johanna. Anybody else sitting at the table that wants to disclose anything publicly? No? Dr. Adamson just joined the group. Do you want to introduce yourself, Peter, please?

DR. ADAMSON: Peter Adamson, from Children's Hospital of Philadelphia.

DR. SANTANA: Thanks, Peter. Peter, do you want to introduce yourself?

DR. HOUGHTON: Peter Houghton, St. Jude Children's Research Hospital.

DR. SANTANA: With that, I will pass it over to Dr. Pazdur for his opening remarks.

Opening Remarks

DR. PAZDUR: Well, I would like to disclose something publicly, my disappointment with Victor and Johanna for not mentioning this but the disclosure is happy St. Patrick's Day.

[Laughter]

As you can see, we in the government have provided you with green folders for the day and, obviously, I am dressed in green but I would like to remind you Pazdur is not an Irish name. The other thing I would like to just emphasize is that Donna and I, as compatriots from Chicago's Polish community, would like to emphasize that St. Patrick's Day is just a warm-up for St. Joseph's Day. Okay?

[Laughter]

DR. SANTANA: Which is Friday, March 19th.

DR. PAZDUR: Thanks for pointing that out.

In all seriousness, I would like to go back to why we are here today, and that is for the subcommittee to discuss two important areas today, one in the morning discussing safety monitoring in clinical studies enrolling children with cancer and then, in the afternoon, discussing nonclinical data to complement clinical data for pediatric oncology.

We look at these as very important

thematic discussions to have. How these areas impact on oncology drug development I think is very important. One thing that I would ask the committee to do specifically is to concentrate really on the pediatric aspect of these. I know that these areas have some tentacles to adult oncology and to other areas of oncology but I would like to remind you that the purpose of this subcommittee is to focus on the pediatric specificity of these issues and special considerations of these broad issues in pediatric oncology.

I would like to thank everyone for being here. I asked Steve what number meeting this is and we think it is the eighth. We may be wrong but we are happy that the committee is meeting on a regular basis. We intend to have the committee meet on a regular basis here and to continue this dialogue with the community. So, Steve, I will turn it over to you.

Introduction of Issues and Agenda

DR. HIRSCHFELD: Thank you. It is customary at the end of remarks to give the acknowledgments but I wanted to give two acknowledgments initially. The first one is to

someone who is in the room right now and I am looking at her, and that is Johanna Clifford who has done I think a marvelous job in helping to organize this meeting, and we have had a number of challenges to overcome along the way, so many challenges that for a period of time we thought we were working under a curse, but Johanna has been steadfast, good humored, competent, rapid in her responses and has been I think a driving force in terms of having the meeting occur as it is and as well organized as it is today. So, thank you, Johanna.

I would also like to acknowledge someone who is in this room, although not physically, but someone who has had enormous influence on our thinking and on our policies toward patients enrollment in studies and in particular children enrolling in studies, and that is Bonnie Lee who has been with the FDA for many years and was associated with the initial hearings of the committee, which was mandated by Congress in the 1970s, to examine the role of children in clinical research. Bonnie has been a particular guide and inspiration for me and also a source of information and direction, which I think has been an asset not

only to the agency but to the country and to all patients. And, I wanted to dedicate the discussion this morning in her honor. So, thank you, Bonnie.

As Dr. Pazdur pointed out, we are going to be discussing the themes of safety and extrapolation. Clinical research, which we have discussed in some detail in this forum over several of the meetings, has been recorded for at least 2,400 years. Children were often the first patients for new procedures and interventions. Part of this evolved from the concept that children were the property of parents so it was rather easy for parents to donate their children for whatever questions might be asked. But along the way there were some founding principles because, unfortunately, children have also been the victims of clinical research.

The founding principles of modern Food and Drug Administration regulation were, in large part, established for the purpose of protecting children and, yet, pediatric therapeutic development has never been as thorough and robust as adult therapeutic development, and most of the people in this room have been part of that process and witness to these inequities. Many therapies are

administered to children without adequate studies and, furthermore, many therapies are not made available for pediatric study until after adult marketing studies are completed and this is particularly true in oncology. So, we have been working to overcome some of these barriers and challenges. And, the challenges are to assemble sufficient data to establish efficacy and safety in the relevant population. The relevant population may be sufficiently rare that confirmatory studies are not feasible, which is particularly the case for many of the childhood malignancies.

There are concerns regarding the implications of adverse events in children and this has been a barrier to the further clinical development of some products because of these concerns. It is also important that there is the establishment and maintenance of a framework that would support systematic clinical investigations for the relevant population. This has been the case historically in pediatric oncology but that framework has always been challenged and is always competing with other priorities. So, it is incumbent on us to make sure that that pediatric research framework has the best resources, and the

best advice, and the best support, and the best regulatory environment to do its job.

The particular issues regarding the safety monitoring in pediatric oncology clinical investigations are an acknowledgment that children require special protections. Yet, on the other hand, there is also an acknowledgment that risk tolerance is higher in oncology therapeutics than in other therapeutic areas. This sets up a potential tension. Furthermore, there are no detailed consensus standards on study monitoring despite numerous international documents describing what could be termed good clinical practice. We will examine those in some detail during the course of the morning. So, the charge to the committee is to suggest ways to incorporate the fundamental ethical and scientific principles in protecting patients enrolled in clinical studies for pediatric malignancies while providing clear guidance and minimizing the resource burden.

We have a series of questions directed toward the committee to help focus the discussion. These are questions which are meant to stimulate what we hope will be an informative exchange and do not have a yes/no or a definitive answer.

The first questions revolves around the principles, what are the principles that should be addressed in safety monitoring of clinical studies that enroll children with cancer? Dr. Kodish is going to provide us with some background on that particular topic. If the principles are adequately stated in existing documents. statutes or regulations, please identify the relevant documents and sections.

The second set of questions deals with the practice. Recognizing that particular populations, disease settings and products may have specific requirements, what general parameters should be monitored for safety in all clinical studies? Or, to rephrase that, what should the default position be for safety monitoring?

Based on the response to the previous question, how often should these parameters be monitored? Again, just giving a framework or guidelines.

Based on the responses to the previous questions, who should do the monitoring? Is it adequate to have the personnel involved in the study be responsible for safety monitoring? When we discuss this in detail we may parse this out

into the type of study, whether it is early development or later development or the type of disease or other risk factors.

What circumstances would benefit from a data monitoring committee? And, are there additional recommendations for safety monitoring?

The afternoon will be devoted to a question which can be traced back to the principle of extrapolation. Extrapolation has been a topic of interest within the Food and Drug Administration for many years. In recent years there has been an FDA working group on pediatric extrapolation that has identified four domains that may provide a basis for extrapolation of adult data to the pediatric population. These are nonclinical data, pathophysiology, natural history of the disease or condition, and response to therapy.

When our group, noted at the bottom of the slide and some of the members are present here in the audience, asked ourselves the question how can we use nonclinical data to inform us about pediatric clinical studies, and in particular pediatric studies in clinical oncology, we realized we needed further background and further discussion before we could have an informed approach to it.

We recognize that the absence of predictive or explanatory nonclinical models in pediatric oncology is today's status quo. We know that safety prediction based on animal studies is estimated at approximately 65-70 percent for cytotoxic compounds and it is unknown for other classes of compounds, particularly the new biologic therapies, gene therapies, immunotherapy, and cellular-based therapies. Efficacy prediction is unknown but low at best. The findings in clinical studies, particularly negative studies, often remain unexplained.

Therefore, further clinical studies that entail resources and risks are undertaken to further the field, and we are posing the paradigm is there a mechanism by which we can use nonclinical data to inform us and improve the clinical research in pediatric oncology. There are potential advantages of using the nonclinical data: a lesser resource burden; the ability to answer questions not amenable to available clinical techniques. There might be ethical or, in fact, legal considerations involved too; possibly a faster time frame to generate data; a dynamic interaction between clinical and nonclinical

findings that can enhance understanding and confidence in results. When we only have a sufficient population to do one definitive study, and that study takes three to five years and it is not feasible to do a confirmatory study, having confidence in those results is critical. The avoidance of non-informative and minimization of negative outcome studies could be another outgrowth and an opportunity for new study designs.

So, the charge to the committee for this afternoon is to provide advice on what types of nonclinical data are considered informative to complement or supplement clinical results. What should the characteristics or properties of nonclinical models and data be to effectively add to the clinical results?

If there are no satisfactory models that exist currently, and we will hear some discussion on approaches, what characteristics should a nonclinical model have to confirm, extend or substitute for clinical results?

Lastly, is there a set of postulates that can be identified, or should a set be developed to help us make the transition for data extrapolation? So, the questions we are asking are what types of

questions that are of potential clinical relevance but are not feasible or acceptable to answer in a clinical study could be addressed by nonclinical studies.

Examples may include the need for repeated tissue sampling, always a contentious issue, particularly in children; the assessment of long-term effects of treatment; effects on reproduction; access to critical anatomic structures, and this is a consideration again particularly for some of the pediatric brain tumors; exposure to toxic reagents; evaluation of non-monitorable or irreversible toxicities; identification of biomarkers for clinical monitoring; and many others which I am sure will come up when we have our learned and motivated panel discuss the issue.

What type of evidence and data would be recommended in each of the following domains to allow extrapolation from nonclinical data and be informative for a clinical condition? There are listed here a few but there may be others. These include, but are not limited to pharmacology and pharmacokinetics, safety, efficacy, behavior, long-term effects, developmental aspects and others

which I am sure will come up.

Are there additional recommendations for the effective use of nonclinical data? For example, will open literature reports be generally acceptable? Is documentation of compliance with Good Laboratory Practice necessary to evaluate animal data? Should nonclinical data be submitted as an independent report with a presentation of primary data sufficient for verification and review? These are all practical questions and we are looking for specific advice.

So, with this charge and these questions before you, I would like to thank all the committee members and our speakers and guests, and everyone who has shown an interest here for participating in this discussion, and I will turn now the further presentation over to Dr. Eric Kodish, who will discuss the fundamental principles involved in clinical research and some of the issues of enrolling children.

Dr. Santana, I think perhaps before we have Dr. Kodish speak--we have some more members of the panel that should be introduced.

DR. SANTANA: Yes. Anybody that joined us a little bit late, could you please identify

yourself into the microphone by name and affiliation, and any potential conflicts that may have arisen since we started?

MS. HAYLOCK: I am Pam Haylock. I am an oncology nurse and I am at the University of Texas Medical Branch, in Galveston.

DR. SMITH: I am Malcolm Smith, pediatric oncologist at the Cancer Therapy Evaluation Program, NCI.

DR. SANTANA: Dr. Grillo, you had your hand up?

DR. GRILLO-LOPEZ: Yes, a point of clarification that I would like to propose to Dr. Hirschfeld. On his first slide on the charge to the committee, which addresses the morning session, you used the phrase "providing clear guidance and minimizing the resource burden" which clearly applies to human resources and financial resources but perhaps doesn't quite stress time. I would suggest that part of your charge to the committee should be that whatever recommendations we propose, and however the FDA understands and decides to apply those recommendations, should not affect the time lines for cancer drug development which today are already intolerably long, and we should be

concerned that the cancer patient in general should not be subject to those too long time lines and that anything we do should, in fact, try to reduce the time lines for approval of new therapies.

DR. HIRSCHFELD: Thank you for your comments, Dr. Grillo-Lopez. I think you touched on one of the themes which is implied. I personally have always incorporated in the concept resource of time because time is, in fact, probably the most precious resource and, if one looks at biology as a broad spectrum, time is something which evolution and biologic processes look to, to conserve in many ways too. So, I thank you for calling attention to the issue of time, and it is incorporated in that specific charge.

DR. SANTANA: One of the philosophic principles of stewardship is that it involves time, people and money resources. So, I think those are all encompassed in your comments.

With that, Eric, are you on line now? Can we proceed with you?

DR. KODISH: I am on line, Victor.

DR. SANTANA: Good. Go ahead, Eric.

Protecting Children in Cancer Research:
What Really Matters

DR. KODISH: Good morning. It is good to be with you virtually, if not physically. I apologize for the inability to get to Washington. We have, hopefully, completed our last big snowstorm of the winter in Cleveland.

I am going to be speaking this morning over the telephone and looking at a Webcast of the slides and this is a work in progress so, please, interrupt me if it is not going well and I will switch to my Power Point presentation. I am looking at the Webcast now and I don't see my Power Point slides yet. What I plan to do is ask Johanna to put on the next slide before I move through them. So, let's give it a moment for me to see the first slide.

I can introduce the talk by saying that I have always thought I had a face for radio and this is an example of that perhaps--

[Laughter]

I see my first slide. the title of this presentation is "Protecting Children in Cancer Research: What Really Matters."

Can I ask that we have the next slide, please?

MS. CLIFFORD: You know what, Dr. Kodish,

if you just want to move on through your presentation--

DR. KODISH: I have it now. Should I go to the Power Point instead?

MS. CLIFFORD: Yes, that would be great.

DR. KODISH: All right, the Webcast didn't work well and I will look forward to joining you on the Webcast after I have done my talk.

MS. CLIFFORD: Okay, there just seems to be a delay.

DR. KODISH: I figured that might happen. The Belmont report I think articulates the key principles of research involving human subjects. My purpose today is to respond to the charge that has been given to the committee and to paint in broad strokes what the key principles are for protection of children involved in cancer research. I think it starts with the Belmont report and the three key principles that are articulated there are beneficence, respect for persons and justice.

The next slide, please. This slide shows a concept of principles that move into practice. I thought it was quite appropriate that the charge for the first half of the meeting talked about both principles and practice. I view the regulations

and their interpretation as a conduit, as a mechanism by which we move from principles to practice. I want to emphasize the word "interpretation" here. I think that the current set of regulations is subject to wide interpretation, as has been pointed out over and over again in the literature. I don't view this as a negative. I think that it allows for thoughtful IRBs, investigators, parents and others involved in the research process to move from principles to practice in an appropriate manner, and that interpretation is really the key step.

The next slide, please. This slide should show a triangle which points out that we are talking today about pediatric research ethics and that this is a more complicated system because of the involvement of a child. The geometry of pediatric research ethics involves parents, on your lower left; the investigator, on your lower right; and the child at the top of the triangle. If we keep the best interests of the child in mind at all points, I think we will be responding to perhaps the most fundamental issue in research involving children.

The next slide, please. This slide shows

a recapitulation of the Belmont principles with an emphasis on beneficence in pediatric ethics. Respect for persons and justice remain important in pediatric ethics but it is my feeling that there is a special place for beneficence when we are talking about children, whether it is research involving children or in clinical ethics regarding children. In fact, more broadly in social policy regarding children it is important to remember that children are not able to vote; don't have economic resources; and we owe an advocacy role I think on behalf of children. It is very important and, to me, prioritizes that beneficence as a concept for pediatric ethics.

Can I have the next slide, please? The principles of medical ethics then are different for children compared with adults. I would say that respect for persons, for good or for bad, has become the dominant principle for adult ethics and this is seen in research ethics where there is a tremendous emphasis on informed consent, and this is out of the derivative concept of autonomy which comes from that principle of respect for persons. By contrast, as I said, I think the best interest of children has to dominate pediatric ethics and

justifies an population that takes beneficence as the most important principles.

I don't want you to move slides back but, if you recall a few slides ago, the slide that shows moving principles into practice, I think beneficence has to be the principle that drives our interpretation of the regulations and our actual practices.

The next slide, please. This slide dissects out some text from the Belmont report. The document itself talks about beneficence as an obligation with two general rules. These are very interesting. It had been sometime since I have looked at them and in preparing for this presentation I found the two general rules cited by Belmont are do not harm and, secondly, maximize possible benefits and minimize possible harms.

On the face of it, these two general rules can be read as conflicting with one another. That is, the charge do not harm is an absolute standard, whereas in the second rule of minimizing possible harms and maximizing possible benefits it is a relative standard and it calls for a weighing of benefit against harm. Again, to put interpretation into play, I think it is the second rule that is

most appropriate for pediatric oncology studies. That is to say, if one is talking about research involving healthy children with no prospect of benefit to that child, the first rule might be more appropriate to apply, do not harm, period. But we are talking about a balance in pediatric oncology and I think the second general rule is more appropriate.

Can I have the next slide, please? If we are on the same page, this slide should continue to cite the Belmont report which says that beneficence is not always so unambiguous and goes on to say that prohibiting research that presents more than minimal risk without the immediate prospect of direct benefit to the children involved limits potential for great benefit to children in the future.

This became, in some sense, the foundation for the different categories of research in subpart D that IRBs are able to approve and points out the key ethical dilemma, as far as I am concerned, which has to do with how we weigh benefits or which benefits count when we are weighing risk and benefit.

The next slide, please. The subtitle of

my talk today is "What Really Matters" and as I thought about a way of presenting this I decided that it could be divided in three phases, what matters before a clinical trial begins; what matters during the conduct of the trial; and what matters after a trial has closed.

One of the members of the panel pointed out the importance of time prior to the beginning of my talk, and I guess this is another way of looking at time as a divider for where the different ethical obligations come in.

Speaking of time, I wanted to get some validation from Johanna. Is the timing going better now with the slides?

MS. CLIFFORD: It is fine, Dr. Kodish.

DR. KODISH: Going fine? Great! So, I would like to now talk about what matters before a trial begins and I could think of at least three important issues. The first is that it be significant science. Again, interpretation is a key here. My view of significant science is that it has the potential to help children with cancer. I think it is important that I am very specific about that. I think that if there are going to be exposures of risk to children with cancer the

potential to help children with cystic fibrosis, for example, may not be considered significant science by this test. The potential to help adults with Alzheimer's disease may not be significant science by this test.

I think that we need to be cognizant of the fact that research involving children with cancer needs to resound back to help children with cancer and that one should look for other avenues to study other important diseases. It is difficult to think of children with cancer as a resource, but I think in some sense this really forces us to do that and, by limiting the risk of exposure to children to that which will come back to help children--and I know that scientifically it is often very difficult to predict in which direction the work will go and how the results will, in fact, play--ut but at the outset one can try to predict and think about a definition of significant as being that which has the potential to help children with cancer.

The second thing that really matters before a clinical trial begins is a risk/benefit assessment. I think in the next several slides I will talk more about what counts as risk and what

counts as benefit.

Finally, it is a study design that will answer the question and that also does not subjugate the interests of any single subject to the overall needs of the research. Again, embedded there are a couple of important ethical principles that I think are perhaps specific--at least the second one under study design--specific to research with a vulnerable population and, as Dr. Hirschfeld said, children certainly are considered and should be considered.

The next slide, please. This slide shows the criteria for the 405 category. As I think everybody is aware, there are four categories of research that can be approved by IRBs under subpart D. Almost all cancer research I think is approved under 405, that is, pediatric cancer research. It is research that involves more than minimal risk but presents the prospect of direct benefit to the individual subject if the risk is justified by the anticipated benefit to the subject; if the risk/benefit ratio is less than or equal to the alternatives; and if parental permission and assent are obtained.

The next slide, please. As we weigh risk

and benefit in research ethics, it is important to remember that risk means risk to the subject but benefit may include benefits to the subject, benefits to other patients, benefits to society or benefits to an investigator or a sponsor. I think what we are aiming for in research involving children in some sense is limiting the benefits that we think about in a risk/benefit analysis so that the benefits that come to the subject are the ones that we are thinking about as we weigh risk to the subject, and that we avoid a situation where children are used as a means to an end. To go back to Emmanuel Kant and the idea that children are valued and protected, I think it is inherent in this sort of balancing.

The next slide, please. This is a slide that looks at some of the issues in early drug development involving children with cancer. There has been a controversy over, what I have put in quotes here, therapeutic intent. The point here is that the prospect of direct benefit is the key ethical and regulatory issue and, in my view, a percentage view of what that potential for therapeutic intent might be isn't that important. That is, I think even a very low chance of

therapeutic benefit for the child should count as a prospect of direct benefit to the child. Again, my interpretation of the word prospect is a very broad one, admittedly, but this is where the issue of interpretation comes in. As the discussion goes on, we can talk about how prospect ought to be interpreted.

The second bullet point you see on this slide has, in parentheses, the potential for 405 creep, that is, moving this issue of commensurate experience that children with cancer have already been through a lot so that it is okay to put them through one more thing. This doesn't stand up in my view as a valid justification for exposing children with cancer to risk.

The alternatives is another key issue that is discussed, if you recall, in the 405 criteria. There needs to be favorable outcome for the child compared to the alternatives.

The next slide, please. If we are on the same page, this should be a slide that says options on top. It has at least three different pathways that families and children can seek out when a child has refractory, untreatable cancer. On your left is a Phase I study; in the middle is

alternative medicine and on the right is hospice philosophy care.

The next slide shows further considerations regarding Phase I oncology research in children. The first is to point out that subject selection is not a major controversy in this realm, that is to say, Phase I studies are done involving healthy children but it is not an issue of wanting to do Phase I cancer research on healthy children. That, to my knowledge, is not a controversy but I put it here because it is important to try to contextualize pediatric cancer research in the broader picture of research involving children. As I said before, I think that Phase I research qualifies, in my mind, as research with the prospect or direct benefit.

Most importantly on this slide, is that potential for benefit mitigates but does not eliminate the need for protection from research risk. To be more clear about that, it is the potential for benefit that is balanced against the risk that mitigates it, but I think the charge to the committee and the work we are going to do this morning is still extremely important. The need for protection from research risk is not eliminated by

the potential for benefit.

The next slide, please. This points out some issues around alternative medicine. The reason that I put this here is that I think there is a yardstick of fairness that we need to keep in mind. It is often the case that when research is being done it is held to a higher standard or a different standard than what is happening in the non-research world, and it is very important I think to the families and the children involved that we try to put this in the lens that they are viewing this off from, and to make it difficult to access research or to have children participate in well-designed, safely monitored research, in some ways, runs the risk of shunting them to alternative medicine where there are vulnerability concerns. It is very prevalent phenomena for children with refractory cancer. I think there are major ethical differences when it comes to children getting alternative therapy compared to adults who can make their own decision. I think we have a very important obligation to prevent harm when it comes to children who are getting alternative medicine, and I think it is extremely important that alternative medicine possibilities be studied in a

rigorous and careful way. But the bottom line is that we need to communicate with families and children. The ones that the research community encounters may also be taking alternative medicine and if we don't know what medications are being taken, then we won't have the ability to study drug interaction with alternative medications and the experimental agent, for example. I just think that it is very important that we keep alternative medicine in mind as something that is out there and we shouldn't be blind to it.

The next slide, please. This slide has a few words about hospice care for children who have refractory disease. Now, some people I think have the experience that those who come to Phase I studies are self-referred, not interested in hospice philosophy care, wanting to continue to pursue anti-neoplastic therapy but, in my experience, that is not the case. In fact, many families who seek Phase I studies also are amenable to having their child get hospice philosophy care. So, the two are not incompatible. I think it is an under-developed approach in children. It is not the main focus of what we are here about today but I felt that it would be incomplete to give this

talk without mentioning that hospice philosophy care should be part of the consent process for Phase I studies.

The next slide, please. This moves from what really matters before the conduct of the trial to during the conduct of the trial. The three items that really matter during the conduct of the trial are informed consent which, in my view, is a communication process in addition to the documentation that happens; ongoing monitoring via a data safety monitoring board, if appropriate, and I understand that much of the discussion later on will have to do with when it is appropriate and when it is not necessary; and ethical action to suspend or stop a study at the right time. It is easier said than done but in parentheses I thought I would say not too soon but not too late either. So, the question of when a study should be suspended or stopped is a key ethical question that happens during the conduct of a study and whether a study needs to be stopped at all. I guess in most cases there is no need to stop it but that question needs to be always asked in the same way house officers always need to ask themselves does this child need a spinal tap. It is a question that is

part of the monitoring process as an embedded function.

The next slide shows the Nuremberg code. This is a quick bit about informed consent. The Nuremberg code said that the voluntary consent of the human subject is absolutely essential. These are slides that I have shown at previous meetings so I think we can go fairly quickly through them.

The next slide asks the rhetorical question of whether we can do any pediatric research at all, and just points out that if the answer is no, that is, if we have to adhere to strict interpretation of the Nuremberg or literal rather than in the spirit of the law interpretation, children as a group will suffer. You saw in the Belmont quotation earlier that there is a clear recognition that there needs to be some research involving children so that we can both protect children adequately but be sure that we make progress in childhood disease.

The next slide talks about three ways of respecting Nuremberg and still doing pediatric research by using parents as surrogates and obtaining parental permission; by involving children when appropriate and obtaining their

assent; and by providing societal protection with IRB approval as the most obvious but also meetings, similar to what we are doing this morning, investigator integrity and other things that provide societal protection for children, we can, I think, ethically do pediatric research.

The next slide shows the difference between parental permission and informed consent and, again, says that the autonomous authorization of an adult--the difference between adult and pediatric ethics is more robust than a proxy decision and points out, from the Academy of Pediatrics, that the responsibilities of a pediatrician to his or her patient exist independent of parental desires or proxy consent. I think that there is a congruent statement that one could make here that says that an investigator's responsibility to his or her subject exists independent of parental desires or proxy consent.

The next slide shows that parental permission is not the oral equivalent of informed consent, and that surrogate decision-making is necessarily less authentic. I am going to skip past the next slide which shows proxy consent,

substituted judgment and best interests, because I think this is familiar ground for most people and we have already emphasized best interests.

I will go to a slide that says informed consent in pediatrics equals parental permission and the assent of the child. Here I want to say that the combination of those two can potentially be more powerful, if done right, than an individual. This has to do with family centered ethics that really seek to care for and do effective communication with a family, which is a dynamic and challenging process, admittedly. But I think both of these issues are very important.

The next slide, please. This provides the regulatory definition of assent, which is a child's affirmative agreement to participate in research. The key point here is that mere failure to object should not be construed as assent. That is, the silence of an older child for research participation can't be interpreted as their assent. Again, there is room for regulatory interpretation here. There is a great deal of controversy around assent and requirements for assent, and I think there is likely to be a fair amount of variability across IRBs with regard to this issue and I would

be happy to discuss this further during our discussion.

The next slide, please. This slide shows some differences between assent in the clinical and research context, and points out the fact that research is supererogatory, that is, as opposed to a clinical context where there is a strong best interests argument to be made. Generally speaking, in research the decision is more voluntary and, for that reason, assent is more powerful phenomenon, in my view, ethically speaking in research than it would be in the clinical context.

The bottom bullet point here is also important I think as a principle perhaps for us to consider, and that is the older the child, the more assent contributes to the ethical justification for the study. This is a problem for diseases that happen in younger children certainly but, all things being equal, an older child I think who can participate in the decision gives us more ethical justification for proceeding in research endeavors.

The next slide just points out a piece of data. This is a scale that we did in our study of informed consent about decision-making preference. It shows everything from, number one, a parent who

wants to leave all decisions to the doctor and perhaps to an investigator, and then a continuum to number five, a parent who wants to make final selection about which treatment their child will receive.

The next slide shows a sample of 108 parents. The reason that I included it this morning is to point out the variability among parents and families when it comes to how they want to make decisions. You see in this slide a large number of parents in the middle, within the green, red and grey columns, who fit into a shared decision-making model. In my view, this is why informed consent is important during the conduct of research. Most people want a shared decision-making approach whether it comes to treatment or research participation and communication. Effective communication is really the key issue for informed consent.

The next slide. As I wind down the talk and get to the conclusion, I want to make the point that the over-interpretation of regulatory concerns can prevent the ethically meaningful participation of children in research.

Can you still hear me?

MS. CLIFFORD: We can still hear you.

DR. KODISH: Great! I heard a beep on the phone. I am going to tell a quick story to illustrate this point. Heather K was diagnosed with a vaginal rhabdomyosarcoma at a children's hospital in the Midwest within the past few months. At diagnosis, Heather had a tumor that was causing intestinal compression. Her pediatric oncologist talked to the family about the diagnosis and then subsequently discussed a Phase III non-randomized study sponsored by the IRS/COG. The family provided informed consent and signed a document at 6:05 p.m. The plan was to begin chemotherapy the following day but the patient developed a bowel obstruction at 11:00 p.m. and chemotherapy was emergently started. At midnight nothing happened that was ethically significant. Clinically, the patient was continuing to get her chemotherapy. But the next morning, when the CRA, the data person, came to enroll Heather in this Phase III study, the RDE, or the remote data entry system, made enrollment impossible. The reason that enrollment was impossible was that the date chemotherapy was started was the previous date and the form would not permit enrollment to happen if

chemotherapy had already been started.

So, what was a well-intentioned regulation system designed to prevent people from being entered on study if consent had not yet been obtained--in fact, in this case everything went perfectly from an ethical perspective but the patient was not allowed to be entered on study. I think that this is a cautionary tale and I wanted to bring it to the attention of the panel today.

Next slide, please. We see many well-intentioned regulatory protections and it is important to realize that they can paradoxically prevent the ethical participation of children in cancer research and Heather's story is one example of that. The physician then needed to go back to the family and explain that, unfortunately, we weren't able to include her as a subject in the research. It wasn't going to change her treatment at all but the future treatment of children with rhabdomyosarcoma in some ways is harmed by the fact that this regulatory mechanism prevented Heather from being a subject in the study. The only alternative would have been for the person doing remote data entry to fabricate and to say that the date chemotherapy was started was the day that she

was being entered on study, and that would have, number one, been an unethical lie and, number two, would have been picked up on an audit if the subject had been audited subsequently though it may have been, in fact, the ethical thing to do because consent was obtained in an appropriate way, it is an important study, and all of the things that we have bee talking about, but the regulatory apparatus prevented an ethical action from taking place and I think it is a disturbing story.

The next slide shows a synergistic approach. The protection of human subjects has been done both through education and regulation and we need to be concerned about developing too much regulation at the expense of education and the expense of thoughtful ethical action.

The next slide just has a few quick points about what matters after a trial is closed. Monitoring for late effects of therapy is an important ethical issue after a trial has closed. The publication of results and dissemination of findings is ethically important. If the science isn't disseminated, then it is like a tree falling in a forest that nobody hears. Finally, the return of results to the subjects who participated is an

ethically under-looked and I think very important issue that symbolizes the partnership that we have with subjects and their families, and I think we need to do a better job than we are doing currently after a trial has closed in getting results back to the subjects.

The next slide shows conceptually the main balance as a point of conclusion in pediatric research ethics, that the best interests of the child-subject are, in fact, balanced against science to benefit others and we need to be cognizant of that balance at all times and be sure that the best interests of the child are not subjugated.

The next slide shows a couple of conclusions. The first is that beneficence, as described in the Belmont report, is the key ethical principle that I believe should guide monitoring of patients in studies. Also, a risk/benefit assessment by the investigator, by the IRB and by others perhaps is more important than informed consent, and that is because I don't think informed consent has the ethical importance in pediatrics that it does in adult medicine, and also because of the relatively ineffective communication process

that is currently happening with informed consent. I would be happy to talk more about that in the discussion.

The next slide shows that the protection of children from research risk and the imperative to improve childhood cancer treatment are both ethically important. The bottom point here is that regulatory fervor intended to protect children currently threatens the ethical conduct of pediatric cancer research, as I tried to illustrate in Heather's story, and we need to remember, I think, that there is an ethical imperative to do work in childhood cancer to improve the care of children with cancer.

The final slide points out that children are both vulnerable subjects who need protection from research risk and a neglected class--and they continue to be a neglected class despite our best efforts--that need better access to the benefits of research.

I thank you all for tolerating the virtual reality nature of this talk and hope that I have been able to make a contribution. Thank you.

DR. SANTANA: Thanks, Eric. Eric, are you planning to stay on line for the rest of the

morning?

DR. KODISH: I am. The only question is whether I should do it by phone or by Webcast.

DR. SANTANA: Okay, because if you are going to stay, then we will just hold the questions for the general discussion, if that is okay with you.

DR. KODISH: That is fine.

DR. SANTANA: But I do want you to stay on the phone line, if at all possible, for the discussion because I think we can communicate better that way.

DR. KODISH: Okay, what I will try to do is watch but mute the sound.

DR. SANTANA: That is fine.

DR. KODISH: Thank you, Victor.

DR. SANTANA: Okay, good. I also want to thank John for advancing your slides on your behalf. Dr. Carome, you are next.

Legal Responsibilities for HHS Supported Studies

DR. CAROME: Good morning. I would like to thank the subcommittee members for inviting me to give a brief presentation on legal responsibilities for studies conducted and supported I think originally by the federal

government and since I speak on behalf of HHS, I have limited it to HHS, the Department of Health and Human Services.

What I am quickly going to do is go over, first of all, the applicability of our regulations. Then I am going to talk very quickly about the major requirements of 45 CFR Part 46, Subpart A, which are the general protections for human subject research. Then I am going to finish up by talking about the major requirements of 45 CFR, part 46, Subpart D, which are the additional protections for children involved as subjects in research.

Again, the regulations I am referencing, 45 CFR Part 46, are the HHS regulations for the protection of human subjects. They have four subparts. The regulations were last revised in 2001. One of the subparts, Subpart B, was revised at that point but most of the regulations remain the same as when they were promulgated more than two decades ago.

So, what is the applicability of these regulations? Our regulations apply in two circumstances. The most common is research conducted or supported by the Department that are not otherwise exempt. That includes clinical

trials conducted intramurally by the NIH or funded by the NIH, as well as many other agencies within the Ddpartment. A second way in which research can be covered by these regulations is research that is conducted at an institution holding an applicable assurance of compliance approved by our office. So, any institution that receives funding from our Department to conduct human subject research must execute a written agreement in which the institution pledges to comply with our regulations, and in that document many institutions voluntarily extend the same regulations to all research regardless of sponsorship. In doing so, the assurance comes to cover privately sponsored research.

This slide demonstrates the relationship and the overlap between the applicability of our regulations and the FDA regulations. You can see that there is in the middle an overlap. The overlap may occur in two circumstances. One is where NIH sponsors a clinical trial or other clinical research, or any research, that involves an FDA-regulated test article. Another circumstance is where an institution, holding an assurance with our office in which they voluntarily

agreed to extend that assurance to all research, is engaged in an industry, privately sponsored research, project involving an FDA-regulated test article.

Very quickly, what are the major provisions of Subpart A? As was previously noted, the regulations, we believe, are clearly founded upon an ethical framework that was articulated in the Belmont report. Its three basic ethical principles, and the fundamental provisions of the regulations can be divided in three groups. One is the provisions related to and assurance of compliance. The second is those related to the IRB requirements, institutional review boards, and the third is those requirements related to legally effective informed consent.

With respect to assurances, the regulations stipulate that each institution engaged in research covered by the regulations and which is conducted or supported by the Department shall provide assurance satisfactory to the HHS Secretary that it will comply with the requirements set forth in the regulations.

The regulations further stipulate specific elements that must be part of an assurance. There

must be a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects. And, the regulations state that those principles must apply to all research regardless of whether or not it is covered by the assurance.

The assurance must designate at least one, and many institutions designate more than one, institutional review board and that must include a list of the IRB members and their relative capacities, and there must be a reference to written IRB procedures. There are requirements related to the IRB and they include specification of what the IRB membership must include, such as at least one person whose primary interests are in the scientific area and at least one member whose primary interests are in a non-scientific area, and at least one member who is not otherwise affiliated with the institution or a member of a family affiliated with the institution.

The regulations have specific provisions related to how the IRB should function and operate; when it must conduct review in terms of initial and continuing review. Then there are provisions

related to expedited review for certain categories of minimal risk research and there are detailed lists of specific criteria an IRB must find in order to approve research. For example, the regulations state that in order to approve research an IRB must find that the risks to the subjects are minimized and reasonable in relationship to the anticipated benefits, if any, to the subjects and the knowledge that is to be gained. Then, there are other provisions for the records that an IRB must maintain.

The last set or provisions in Subpart A deal with legally effective informed consent. They include an introductory paragraph that talks about the general requirements. For instance, no investigator may involve a human subject in research unless the informed consent of the subject or a legally authorized representative of the subject has been obtained, except in certain limited circumstances in which informed consent can be waived.

The regulations go on to stipulate basic elements that I think most people are familiar with: the nature of the research; the reasonably foreseeable risks; the reasonably foreseeable

benefits, if any, to the subject; and others, such as alternatives that a subject may choose instead of entering the research. The regulations stipulate that consent must generally be documented, except in some limited circumstances. Then, there are waiver provisions both for obtaining informed consent at all or for documented informed consent, and I won't go into those in detail.

Let's turn finally to the provisions for research involving children under Subpart D, the additional protections for children. Again, this is a subpart that is unique to the Department of Health and Human Services. Whereas all the Subpart A provisions that I just went over have been adopted by other departments and agencies, Subpart D has only been adopted by the Department of Education in addition to our department.

Subpart D applies to all research involving children as subjects conducted or supported by our department. It is important to note that there is a specific definition of children in the regulations, and they are persons who have not attained the legal age for consent to treatments or procedures involved in the research

under the applicable law of the jurisdiction in which the research will be conducted. It is important to note that in order to then understand who a child is with respect to the research regulations, you must understand state and local law that defines who can consent to what and at what age. Therefore, a child in one state might not be a child in another state for the purposes of these regulations.

The Subpart D requirements in general--first of all, you have to satisfy all the requirements of Subpart A. So, if a research project involving children doesn't satisfy some provision of Subpart A, then it is moot about the additional provisions. The research would not be approvable. But if the research is approvable under Subpart A, there are additional requirements of Subpart D which must be fulfilled and satisfied.

As Eric referenced, there are four categories of research that are approvable under Subpart D under our regulations. These are primarily scaled to risk versus benefit as you walk through each of these categories, and I am going to do that very quickly.

The first category, 404, is research not

involving greater than minimal risk, and minimal risk is defined in Subpart A. In order for this research to be approved under this category, an IRB must make one general finding. It must find that there are adequate provisions for soliciting the assent of the child and permission of the parents or guardians, as set forth in Section 408.

The next category, Section 405, which Eric went into more detail, is research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. So, the benefit has to be tied to the subjects as opposed to society in general and the knowledge to be gained. Here, the IRB must make three specific findings. The IRB must find that the risk is justified by the anticipated benefits to the subject; the relationship of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternatives outside the research context; and, again, the same provisions for assent and permission apply throughout these four categories.

The next category, 406, involves greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield

generalizable knowledge about the subject's disorder or condition. For this category there are four criteria that an IRB must find. They must find that, first, that the risk represents a minor increase over minimal risk. Whereas minimal risk is defined in the regulations, what a minor increase means is not defined so that is left up to the judgment of the IRBs.

Next, the IRB must find that the intervention or procedure within the research presents experiences to the subjects that are reasonably commensurate with those inherent in the actual or expected medical, dental, psychological, social or educational situation of the child. Commensurability is one of the factors that Eric touched on but applies only in this category, 406.

The next two provisions--the IRB must find under 406 that the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition. I think the key words here are that you have to understand that the child must have a disorder or condition, two terms that are not otherwise defined in the

regulation and are of vital importance. So, it is sort of a higher standard than the usual generalizable knowledge standard that probably applies to research under Subpart A only. Lastly is the assent or permission provisions.

The fourth category and final category is research that is not otherwise approvable under one of these four categories which presents a reasonable opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. For this, the IRB still must review and assess the research with respect to Subpart A and D, and must find that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious health problem affecting the health or welfare of children.

The project is then forwarded to the Department. They come through our office and we act on behalf of the Secretary to process these. In order for the research then to be approved, the Secretary, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, must determine either that the research in fact

satisfies one of the other three categories, 404, 405 or 406 or, if not, three things must be met: that research presents a reasonable opportunity standard that I previously went over; that the research will be conducted in accordance with sound ethical principles, and hopefully that is something that applies to all research conducted; and adequate provisions for the assent of the child and parental permission.

Finally, there are some additional provisions of Subpart D that are provisions related to soliciting assent, and assent is not always required and an IRB may determine it is not warranted, particularly under category 405. There are provisions for soliciting permission of parents, and the regulations speak to whether you need both parents' permission. If the category is 405 one parent's permission is sufficient but for 406 or 407 two parents are required, except in very limited circumstances.

It is important to note that there are provisions for waiving parental permission or guardian permission. Just like informed consent can be waived under Subpart A for research involving adults, parental permission can be waived

in certain circumstances and this is I think unique to our regulations and not found in the parallel regulations within the FDA.

Finally, there are specific protections for subjects who are wards of the state or any other agency, institution or entity for research approved under 406 or 407. Among those requirements, there must be a specific advocate appointed for each child who is participating in such research who is a ward.

In summary, I have quickly tried to go over the applicability of our regulations and contrasted that with the FDA regulations applicability. I have gone over the major requirements of Subpart A of our regulations and finished up with a discussion of Subpart D, and I thank you for your attention.

DR. SANTANA: Thanks, Dr. Carome. Dr. Hirschfeld?

Legal Responsibilities for Studies with FDA Regulated Products

DR. HIRSCHFELD: I would also like to thank Dr. Carome and note that when he was wearing a uniform which was a color more consistent with the theme of the day, he was the head of the IRB at

Walter Reed Army Medical Center. I also want to thank him for his efforts on clarification of the regulations in ongoing discussions as they apply to pediatric oncology, and he has taken a leadership role in the Office for Human Research Protection in that regard.

I am going to even more quickly, I hope, go through the FDA regulations. One might ask what is a pediatric oncologist doing talking about FDA regulations, but that is one of the strengths of the FDA, that there are wonderful opportunities to be involved in many aspects or research in clinical medicine, including the development of regulations. I was on the working group that developed the Subpart D and, in fact, wrote the first draft of that document.

As Dr. Carome pointed out, there is some overlap, and these slides have a lot of data which is intended for reference and I will not go through all the aspects of all the slides, but just to note that there are laws synonymous with an act or statute which are developed and passed by the Legislative Branch and signed by the President and these are published in the United States Code. Then there are regulations synonymous with rule,

and these are developed and published by the Executive Branch, the various departments and agencies within the Executive Branch doing the detailed work, and these are published in the Code of Federal Regulations, which is referred to as the CFR.

The FDA authority is derived from multiple laws and regulations, and the focus is on product and product use. There are a number of applicable regulations for good clinical practice in the research setting, and these include the human subject protection, which is in 21 CFR, Part 50; financial disclosures, which is in Part 54; institutional review boards, which is in Part 56; and investigational new drugs, which is in part 312.

Part 50 has actually three sections to it. One is reserved for future use and Part D, you will notice, is the additional safeguards for children in clinical investigations, which is the focus of the discussion now.

This is a catalog of all the various sections within Subpart D of 21 CFR, 50. You will see that there is mapping and harmonization between the relevant sections of the HHS regulations.

Now, the relationship--and this is just a textual representation of the schematic that Dr. Carome presented--is that FDA regulations apply to all research using FDA-regulated products. In contrast, the HHS regulations apply to all research that is supported by HHS. Research that is supported by HHS using FDA-regulated products is subject to both sets of regulations, and the regulations are harmonized although there are some differences which Dr. Carome elaborated on earlier. The definitions, you will see, parallel those definitions in the HHS regulations and put the onus of interpretation on the local jurisdiction and on the local IRBs, and that is the theme that persists throughout these regulations. So, these definitions are included here to show that there is harmonization and in some cases, we believe, some clarification because the scope of FDA-regulated research is, in many ways, different and can apply to domains where HHS research is not applicable. So, it was important to have not only clarity on the definitions but consistency and, therefore, there are definitions that are included here so that there is not, we hope, much ambiguity in terms of how to apply and interpret these regulations at

the local IRB level.

Here, again, there is an emphasis on the concept that Eric Kodish developed for us a little earlier this morning, and that is children do not actually engage in a consent process. Their parents provide permission for them to participate in the research. Then, there is the same emphasis as in the HHS regulations that the child must at least be approached for assent.

So, in addition to the other responsibilities assigned to IRBs, the FDA regulations ask that the IRB review clinical investigations involving children as subjects covered by Subpart D and approve only clinical investigations that satisfy the criteria which are described in Subpart 51, 52, 53 and the conditions of all other applicable sections of Subpart D.

These are again mapped to the four risk categories which were developed in the 1970s and which, because of their serviceability and their flexibility, have been maintained to this date. These, again, discuss the concept of minimal risk here with specific examples of how it applies to pediatric research.

Since the IRBs are a conduit through which

research occurs, there are specific instructions on when IRBs may approve clinical investigations, and these are divided into the specific risk categories. So, there is greater than minimal risk under 50.51. In 50.52 there is greater than minimal risk presenting the prospect of direct benefit and the conditions, again, are analogous to the HHS regulations; and 50.53 shows that the IRBs can approve clinical investigations involving greater than minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge about the subject's disorder or condition, and the same caveats about having a disorder or condition and having the prospect of generalizable knowledge apply, and these are addressed in some detail.

In addition, there are IRB approval criteria which are explicitly stated and these include not only minimization of risk and that the risks are anticipated in relation to the benefit, but that the informed consent process is adequate and appropriately documented and looking for safeguards. That is going to be theme which we are going to look at in detail, what safeguards can be and ought to be implemented.

Subpart D addresses this explicitly.

There is a paragraph devoted to monitoring which I will quote briefly: While the level of risk in a clinical investigation may change during the course of a study, appropriate strategies may be included in the study design that may mitigate risks. These might include exit strategies in the case of adverse events or a lack of efficacy, or establishing a data monitoring committee to review ongoing data collection and recommend study changes, including stopping a trial on the basis of safety information.

Part 56 addresses institutional review boards, and the general provisions and organization are discussed in the first part; IRB functions and operations in the second part; records and reporting in the fourth part; and the administrative actions for non-compliance in the fifth part.

Now we come to the IND regulations, 312 Subpart A, which are the general provisions which are outlined here.

Subpart B, which are in essence the mechanics of an investigational new drug application and the obligations under those sections.

Subpart C, which discusses the administrative actions, and Subpart D which goes into detail of the responsibilities of the sponsors and investigators.

There is a Subpart E, which doesn't map explicitly to other HHS regulations, which addresses the drugs intended to treat life-threatening and severely debilitating illnesses which apply to pediatric oncology studies. You will notice in the various paragraphs here that in 312.87 there is a requirement for active monitoring of conduct and evaluation of clinical trials. It reads, for drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress. So, this places an FDA role in a dynamic way in the research being conducted in the realm of life-threatening illnesses.

In addition, 312.88 has specific safeguards for patient safety which refer back to the other sections that were discussed, Parts 50, 56, 312. We didn't discuss 314 which is the NDA regulations and 600 which apply to the biologics

but there are analogous regulations in these areas.

I will just abstract from here that this includes the requirements for informed consent and institutional review boards, and that these safeguards further include the review of animal studies prior to initial human testing; the monitoring of adverse drug experience through the requirements of IND safety reports; safety update reports for marketing and postmarketing.

So, our conclusions from this section are that the FDA has authority to regulate clinical studies using FDA-regulated products; that FDA regulations incorporate both IRB and FDA oversight of studies; that regulations exist for studies using products intended to treat life-threatening illnesses; and that regulations exist for providing additional safeguards for children enrolled in clinical investigations; and, as noted, HHS and FDA regulations are intended to be harmonized. Thank you.

DR. SANTANA: Thank you, Dr. Hirschfeld. I think we will hold our questions until we reconvene at the point for discussion. I think we are just a few minutes behind time. We will take a 15-minute break--Dr. Hirschfeld wants a 10-minute

break. We will take a 10-minute break and try to reconvene at almost 9:45. Thank you.

[Brief recess]

DR. SANTANA: We will go ahead and get started with the second part of the morning presentations. To initiate that, Dr. Anderson, from CTEP, will be our next speaker. Barry? Eric, are you back on board?

DR. KODISH: I am here.

DR. SANTANA: Thank you, Eric.

Enrollment and Monitoring Procedures for NCI Funded Studies

DR. ANDERSON: I am Barry Anderson, from NCI CTEP, and I want to thank the FDA and Steven for inviting us to provide information about the enrollment and monitoring procedures for NCI-supported clinical trials.

For pediatric cancer clinical trials, the appropriate enrollment of the individual patient, the child who is going to come onto the trial, as well as the monitoring of that individual patient's experience during the trial and the cumulative experience of all children who are involved in a clinical trial I think are necessary components in terms of trying to enhance the patient safety and

the scientific validity of the trial itself.

So, at the onset, from NCI's point of view, it is important to work to assure that each child accrued to a trial is receiving the appropriate treatment within the clinical trial itself, and that monitoring that is associated with the trial monitors the toxicity and effectiveness of the treatment intervention within each clinical trial both for that individual child, as well as for the trial overall.

The words "safe" and "effective" can be applied to many of the standard treatments we use in pediatric oncology to treat various childhood cancers. These words have special meaning in pediatric oncology. As Dr. Kodish mentioned, there is a special sort of risk/benefit ratio that we always consider because, while therapy for childhood cancer is often successful and that is something that differs from much of medical oncology, the therapies that we use are always toxic in pediatric oncology and they always carry a risk of treatment-related morbidity and perhaps even death in many cases.

So, selecting the proper treatment I think is essential because compared with other serious

childhood diseases, such as asthma or cystic fibrosis, childhood cancer includes many distinct histologic diagnoses, and each tumor histology requires a distinct treatment appropriate with its own risks and benefits. The chances of cure also diminish quickly if the proper therapy is not used at the outset. That differs, I think, from some of the other more chronic diseases that are serious within childhood diseases but can have chances to change the therapeutic approach over time.

In regards to enrollment, a question for the clinical trials done in pediatric oncology is who should be enrolled. Pediatric oncology has evolved an approach of risk stratified treatment regimens and within each tumor histology the patient characteristics and the tumor characteristics establish a risk of relapse. This risk of relapse then is used to stratify the treatment assignment for each child in terms of the type of clinical trial or the specific clinical trial they would be appropriate for. Using this risk of relapse the intensity of the treatment that the child receives--and for intensity you can also say increased toxicity--is then set to best fit the child's cancer. So, it is vital to treat the

child, as best we can ascertain at the time they first present, according to the appropriate treatment regimen.

By following this treatment stratification approach, the goal in pediatric oncology is to minimize the exposure to highly toxic therapies for those children who don't need that much treatment, in a relative sense, and also for the oncologists to have some comfort in knowing that another child who has a high-risk chance of relapse, that they will in fact potentially benefit from using a more intensive and more toxic treatment regimen.

To apply this treatment stratification approach across an entire clinical trial, it is important that the eligibility criteria within the protocol by which all the patients are brought into the trial--that those protocol eligibility criteria are clear in regards to the clinical characteristics of the patient and the pathologic and biologic characteristics of the tumor--that all these characteristics are clear and easy to understand.

The pediatric oncologists that are involved in the trial and who would be enrolling patients must be properly informed on how to apply

the eligibility criteria that are presented in the eligibility section of the protocol itself. If anyone has ever had experience in trying to bring a patient with rhabdomyosarcoma into a sarcoma trial, it can be a be very complicated endeavor and many mechanisms have been put in place to assist the pediatric oncologist to make sure that the proper decision is made in terms of treatment.

As technology has advanced, eligibility criteria have moved beyond what they have been in the past, just being tumor histology and perhaps the staging of the patient. As histologic and biologic characteristics of tumors are better defined and refined, we also are incorporating in many cases in pediatric oncology central input on the pathology and biology, such that central review of the patient's tumor pathology and diagnostic biology assays are used to improve the likelihood that a child receives the best available therapy for their specific tumor pathology and for their risk of relapse.

This has been used in a variety of tumors in pediatric oncology in the recent past. With rhabdomyosarcoma there is central review of alveolar versus embryonal rhabdomyosarcoma

pathology that is used basically in real time so as to assure that the patient goes on the proper risk-stratified treatment regimen. For neuroblastoma there are a variety of biologic characteristics that make amplification and other genetic changes that are characteristic to each tumor, and that is also looked at in real time. For Wilms tumor there has been a central review of that tumor histology for favorable histology versus focal or diffuse anaplasia that all distinguish patients for their appropriate trial, and there are a variety of genetic studies that are done, both centrally and locally, to establish the appropriate treatment for children with acute lymphoblastic leukemia, the most common diagnosis in childhood cancer.

Phase I and pilot studies also have specific eligibility criteria. In these cases, it may not necessarily be the case that you need to be concerned about the tumor histology so much, especially in Phase I where a child has already received treatment, but it is important to ensure that those patients who are enrolled in a trial have no other treatments that provide a reasonable potential for cure or substantial clinical benefit.

For patients who have newly diagnosed tumors but have a type of tumor that historically has a poor response to therapeutic interventions, we want to make sure that any sort of pilot treatment interventions that have been tried balance appropriately the benefits and likely risks in the child's prognosis. So, before considering trial monitoring we consider that getting the right patient on the right trial is vital given the stratified approach we have to treatment in pediatric oncology.

NCI supports a variety of investigator groups to do clinical trials in children with cancer. The largest is the Children's Oncology Group, which pretty much every pediatric oncologist in North America is a member of. That is the group that does the Phase III studies primarily as well as Phase II studies and pilot studies. There is the COG Phase I Pilot Consortium that is a smaller group, about 20 institutions, that is assigned to do Phase I studies. The Pediatric Brain Tumor Consortium I think is around 10 institutions as well. Their focus is on newer therapies for brain tumors in children. The new approaches to neuroblastoma therapy is a program project grant

that NCI supports that is now 12 or 14 institutions I think, focused on early phase studies for children with neuroblastoma, high risk neuroblastoma. There are also individual grants to investigators that may include clinical trial research.

All these, because of the nature of pediatric oncology and the relative lack of number of patients, are usually multi-institutional. Given that they are multi-institutional, that brings on special responsibilities in terms of trying to conduct a trial at multiple sites simultaneously and trying to have all the investigators that are enrolling new patients and treating ongoing patients aware of what is going on with the trial. So, the NCI has worked with these various groups that we support to facilitate this sort of intake of information and distribution of information.

The investigators that are part of these various groups are committed to report toxicities, the regimen delivery and the ability to deliver the regimen as defined in the protocol and the response data in a timely fashion. Some things such as remote data entry have been put in place now to

help facilitate that. There is a data center assigned with each of these groups that we support that is capable of readily receiving the data, analyzing the data and then reporting important data trends to the investigators, be it the study committee and perhaps beyond if necessary. There is an operations office component. They are able to communicate with investigators continuously throughout the clinical trial by email, by web site, by the phone, etc. There is sort of this continuous back and forth going on between the investigators at the local institutions and a more centralized body that is helping to run the trial.

In terms of monitoring, again it starts, I think just like enrollment, at the individual child level where there, is within the protocol, guidance provided to the local institutional clinicians as to what sort of laboratory results for tumor-related or treatment-related abnormalities need to be done and at what interval. There are radiologic characterizations of the tumor and the consequent organ dysfunction that are also asked for in terms of the initial diagnosis of the child and then subsequently during their course of treatment. Then there are interval evaluations to

establish the tumor response to the treatment interventions that are being conducted during the study.

The protocol--and we look for this at NCI when we review the protocols that come to us--must provide sort of a consistent and uniform approach to all these aspects of monitoring of the individual patient. The frequency by which these studies are performed would be consistent with or greater than good clinical practice. Because the children are on a clinical study, oftentimes they get more frequent monitoring of some of these aspects than they would if they received standard of care treatment off the protocol. But, again, it depends on the intervention that is being undertaken and the specific tumor diagnosis under consideration.

When you accumulate all this information, the monitoring and the clinical trial itself, that is where some of the infrastructure that NCI supports comes into play because, as I mentioned before, it is very important that patient data is submitted at protocol-defined intervals; that the data is accumulated, analyzed and then reported; and then that the significance of this data, be it

the toxicity data or the effectiveness data, is interpreted so that appropriate patients are being accrued to the study; that treatment toxicity is acceptable and that there is some efficacy of the treatment interventions as defined in the protocol beforehand.

There is some debate and discussion and variability in terms of who and how often this data that is accumulated and reported on is reviewed. Within NCI, we work with the guidelines established by NIH for data and safety monitoring and these requirements call for the oversight and monitoring of all human intervention studies to ensure the patient safety and the validity and integrity of the data itself for the study. The monitoring in the study is to be done at sort of a level that is commensurate with the risks and size and complexity of the clinical trial.

The oversight monitoring under Phase III clinical trials, which many of the pediatric oncology trials are, calls for the establishment of a DSMB. The DSMB, according to NIH, is also appropriate for Phase I and Phase II clinical trials if the studies have such things as multiple clinical sites, are blinded or masked or employ

particularly high-risk vulnerable patient populations. In pediatric oncology we sort of hit throughout this so we call for sort of the default to be towards some sort of formalized monitoring committee for most of the studies that we do.

The NCI, in response to NIH sort of formalizing its approach to data and safety monitoring, in the not too distant past has finished reviewing all the data and safety monitoring plans for the cancer centers that NCI supports across the country. That was I think an education for both NCI as well as for the cancer centers, for them to really kind of fess up and look at what they actually do in terms of the monitoring; what goes on in their human subject clinical trials within their cancer centers. But they all submitted them and they were all reviewed.

Some of the key, essential elements for these monitoring plans that we had to consider, and that then subsequently have also been extended to some pediatric groups, are the monitoring and progress of the trials and safety of the participants; the plans for assuring compliance with adverse event reporting; and plans for assuring that data accuracy and protocol compliance

are performed.

As I mentioned, while in pediatric oncology basically we don't work from a cancer center model, we work more in a multi-institutional approach so it is a more distributed coverage in terms of who is performing the trials. Nevertheless, these particular essential elements were taken on by pretty much all the groups that we have that I mentioned earlier that NCI supports in one form or another, again, moving to the default of having some sort of more formalized data monitoring committees for all the trials.

The composition of the DSMB and the various data monitoring committees may differ between the different groups that I mentioned that NCI supports for pediatric oncology but the goal is the same, and it is to have capable and informed observers be responsible for the oversight of the trial. The reviewers are people that are outside of, and in addition to the study committee, and they evaluate the trial data at regular intervals to monitor the treatment toxicity and the effectiveness of the treatments that are being used. Then, the review determines whether the continued accrual to the trial is safe and

appropriate. COG itself has two DSMBs, one for solid tumors and one for the leukemia and lymphoma studies, and they meet twice a year, each one of those DSMBs, to go over the studies. Actually we go over pilot, Phase II and Phase III studies in those sessions. The Phase I Consortia also has a DSMB that meets twice a year to go over all those Phase I studies. In addition to the Phase I Consortia, the PBTC and the NANT, all of which have a DSMB type of component, have more frequent discussions with the groups that are beyond just the study investigator and any sort of data personnel or statistician directly involved. They have a discussion of their studies sometimes on a weekly basis, sometimes on a monthly basis, and sometimes it also includes people from outside the group itself to overlook what is going on with their particular studies.

In terms of compliance with adverse event reporting, another one of the essential elements that NCI has, NCI-funded studies use the adverse event expedited reporting system, or the AdEERS system to report toxicities. This is a computerized system that is available now to all the funded groups with which they can fairly easily

report adverse events that occur during their clinical trials. That data can then be accumulated easily within their group, but also important things can be sent off to the FDA or to drug sponsors or the NCI as appropriate, especially for studies that involve IND agents.

Then, it is the institutional principal investigator that is ultimately responsible to assure that the AEs are reported in a timely manner. Whenever we review the cancer center approaches, they list out that sort of the CRA should submit this and then there is a nurse practitioner or someone that is behind the CR to make sure it gets submitted, and at some interval the principal investigator locally is responsible to make sure that all the AEs that may have occurred had been properly reported.

Finally, for assuring data accuracy and protocol compliance, the cooperative groups and these consortia practice ongoing quality control and interval quality assessments such as by using institutional audits. This has been something that has been ongoing throughout the creation of each of these groups.

In summary, NCI has worked to establish a

framework to allow appropriate monitoring and oversight of pediatric oncology clinical trials. To address some of the issues that Steven had brought up before in terms of the general parameters that we look at, we first want to make sure that the enrollment of patients is appropriate to the diagnosis and risk of relapse for the patient or the availability of standard treatments for recurrent and relapsed disease, and that laboratory and radiologic monitoring for toxicity and response to treatments is established within the protocol before any patients are accrued.

The frequency of monitoring would be equal to or greater than standard of care for the individual patient that is enrolled on a clinical study, and there would be continuous protocol monitoring by the study committee because they receive this data on a daily basis. There would be interval protocol monitoring on a monthly to biannual basis, depending on the risk and specifics of the trial, by a group outside of the study committee itself.

Who does the monitoring? The daily monitoring is by the study committee itself. The interval monitoring usually involves concentrations

and statisticians that are not directly involved in the trial.

When is a data monitoring committee needed? For Phase III studies you need a DSMB. For multi-institutional trials you need to have a monitoring committee for high-risk populations. You need to have a monitoring committee for complex treatment. For studies with early stopping rules, which many pediatric studies have, you have to have a monitoring committee. With conflicts of interest, which may not be as much of a case in pediatrics as it might be in medical oncology, you need to have a monitoring committee.

I think that with pediatric oncology trials we hit many of the points that are brought up by various agencies of situations where a monitoring committee is required so that virtually always in pediatric oncology some sort of monitoring committee is involved in the oversight of the practices of the group, as well as the conduct of individual clinical trials. Thank you.

DR. SANTANA: Thanks, Barry. Before I stand up to give the last presentation of the morning, we have an opportunity for an open public hearing. So, if there is anybody in the audience

that wishes to address the committee, this is the opportunity to do so. I would ask that if you are going to do that you come to the front of the room to the podium and identify yourself by name and affiliation.

Open Public Hearing

MR. RAKOFF: Wayne Rakoff, Johnson & Johnson. Just a quick question, that came up this morning that I would like to hear discussed during the discussion, is with regard to the FDA guidance on data reduction in oncology trials. It would be important to us to know if there are any variances in that with regard to pediatric studies.

DR. SANTANA: Steve or Rick, do you want to address that now or do you want to address it during the discussion period?

DR. HIRSCHFELD: We can address it in a little more detail but, in brief, that is a global commentary and there isn't a specific pediatric component to it. I think that is a good suggestion that maybe we should consider in the future, a pediatric specific component.

DR. SANTANA: Any other comments from the audience?

[No response]

Monitoring Procedures at a Private Children's Hospital

DR. SANTANA: First of all, I want to thank Steve, Richard and the rest of the FDA for always bringing the pediatric oncologists to set examples in these initiatives. I am personally very appreciative of all the efforts that we have had on behalf of the issues that we deal with in pediatric oncology.

My task this morning, as I was charged to do, is to bring a perspective from a private institution with the caveat that St. Jude really is an NCI cancer designated center so a lot of what we do in terms of our own monitoring is reflective of what we have to do to comply with the NCI regulations.

What I would like to do over the next 20 minutes or 25 minutes or so is talk to you about two issues. One is how we set forth monitoring of our St. Jude studies--not the cooperative group studies for which we still have to comply with COG, but our own intra-institutional studies that follow a parallel system to the NCI monitoring plan, and what that monitoring plan involves and what parameters we have designated for monitoring.

Then, a bigger part of my talk will be on a project that Don Workman and I worked on in terms of trying to handle adverse event reporting within the institution and tried to develop an interactive web-based model to try to get a handle on that.

With that, I will go ahead and get started. As Barry has already said, monitoring of trials is really an ongoing, continuous review of the conduct of the trial. For the purpose of distinction, I will make the note that to me monitoring occurs while the study is ongoing. Whereas a lot of people use the word auditing, to me auditing is a post facto thing that happens after the study has been completed. Then you go back and see if the study was conducted the way it was supposed to be; if the data is good enough; if there is quality in the data; and if there have been any other issues that occurred during that post facto process. So, to me, monitoring occurs real time whereas auditing occurs after the study has been completed.

Monitoring is really a shared responsibility of many individuals. We always talk about monitoring being the responsibility of maybe one particular group but at St. Jude we have the

notion that this is really the responsibility of the research team. We always talk about the principal investigator but it is really the research team. The research team has many components to it of which, hopefully, the principal investigator is the lead person but there are research nurses, there are CRAs, there are other members of the study team who also have responsibility for this process.

Institutional officials have a major role in this, not only in terms or providing infrastructure resources to conduct some of this monitoring, but also to set a culture and example that is transparent to make sure that things occur very openly and that everybody is knowledgeable about what is happening. Then, the oversight committee--you heard a little bit about DSMBs which I won't talk about and IRBs and other committees that may be involved in this process.

Eric had a little figure this morning of a triangle. I didn't know he had a triangle so I brought a triangle too, but my triangle is a little bit different. It makes a different point. The point of this triangle is that in the center of the process are the participant in the research but

there are many other people involved in this whole process in which, as I mentioned to you earlier, the partnership includes the investigator, the research team, the IRB, other oversight committees and then institutional officials. So, I view this more as a partnership, not just the responsibility of one individual.

One of the things I want to cover is point number one and point number three on this slide, which is how can we systematically approach some of these problems in terms of monitoring and adverse event reporting.

So, I think the first step whenever you deal with a promise to define a problem in this case is what needs to be monitored and what needs to be reported. I think that is a good point to start and I will talk about that in a minute; then, dividing the role, the different committees that provide some of this oversight and I really won't go into detail on that although I could during the discussion if anybody has any questions; and, lastly, developing an infrastructure to allow this to happen so that the reporting occurs, that there is a process of evaluating the reports, and then a process of acting in a timely manner when there are

concerns. So, that will be the latter part of my talk.

As I mentioned to you, we are an NCI cancer designated center so we also had to comply and submit an institutional data safety monitoring plan to the NCI a few years back that was reviewed, approved, etc., etc., and now we provide our monitoring under the umbrella of what that plan says.

So, the first thing was to define what elements we were going to monitor. So, we have kind of followed the parallel system that the NCI designated in the clinical data update system of what data should be collected. We look at patient specific data, the demographics, date of birth, gender, those things that we have to collect; the date of entry into the study; the treatment status, if the patient has been previously treated, on what protocols and what therapy the patient was on; and, if they were off therapy, for what reasons. All that gets captured as part of the monitoring of the patient on the study.

Then, there are subgroup data elements that are also captured. Barry mentioned, very appropriately in his talk, the issue of eligibility

and determining that the right patients go on the right studies. One of the things we have done at St. Jude in the last ten years is we have established a separate office, which is called the protocol office which is actually an office that provides the infrastructure to help investigators deal with many of these issues. The protocol office, obviously, is manned by a group of people and one of the responsibilities, for example, is that when an investigator enrolls a patient on a study we have to fill out electronically an eligibility check list. The eligibility check list gets faxed to that office and a patient-specific consent is generated for that patient on that study. So, right at the beginning there are some checks and balances in terms of the eligibility of the patient so that the right patient is put on the right study and the correct consent is used for that patient. So, that is an ongoing process that occurs early on during the trial and the patient enrollment of the trial.

Once the patient receives the therapy, they monitor the cycle or the course of therapy. If is a Phase I study, what dose level the patient is currently being treated with; the start date;

some other parameters like BSA and weight. They monitor, particularly in Phase I studies, the agent; the dose of the agent; if there have been any modifications, why there have been modifications. We will talk a little bit about adverse event reporting later on. Then, as part of the monitoring during certain periods of the trial, the patients will be monitored in terms of response because the trials will have stopping rules based on response, not only in terms of toxicity but also in terms of response so a Phase II trial that has some response built-in stopping rules will be stopped at the right point once the monitoring is occurring in terms of the response that has been achieved.

I tried to summarize this in two or three slides. This is kind of how we do it at St. Jude in terms of our own institutional Phase I/Phase II. We don't do many Phase III but we do have an auditing plan for Phase III studies and for some studies in which we hold the IND.

So, for Phase I studies the central elements in terms of demographics, eligibility and informed consent, that is monitored continuously. It is monitored continuously because I told you

that there is a check at the beginning in terms of eligibility and in terms of informed consent that occurs in real time when the patient gets registered. So, that is done continuously as the patients go on a study in a Phase I study.

The protocol office also is monitoring the study in terms of the data elements for the study so there are templates very similar to the RDE system that is developed by COG, templates of data capture forms. Those data capture forms are electronic and the monitor on a monthly basis that he or she is assigned will go through those and will see if there is data that is missing. If there is data that is missing, a report is generated to the principal investigator that data is missing on a monthly basis. So, it is a good system in terms that it keeps the research team kind of continuously on top of making sure the data is being collected.

On a quarterly basis for a Phase I study there is a report that is generated. I will show you in a minute where the reports go but, in a nutshell, it goes, obviously, to the principal investigator and to the research team, and then it goes to the subcommittee of the scientific review

committee that also oversees monitoring to make sure that they are separate from the protocol office and from the investigator looking at this data.

Then, for every Phase I study that we are the primary sponsor of at St. Jude, the first three patients enrolled in the study are monitored. Then, once the first three patients are monitored, one additional patient per dose level is monitored in real time. The idea of doing the first three patients is that in many studies usually within the first three patients you know if your systems are in the right checks and balances so that you want to monitor those first three patients very acutely so if there is a problem with the system, with the templates, with potentially things not going right, you can pick it up very quickly and make the right adjustment so that for the subsequent dose levels, if you monitor one patient in real time, you should have resolved all of that.

We do a lot of Phase II studies at St. Jude and we also do the eligibility, essential elements and consents as outlined here. We also do missing data reports on a quarterly basis. Obviously, in Phase II, just like in Phase I, you

are interested in adverse events and those are reported quarterly. Then, on a semiannual basis the monitors will verify the coding of response so that the studies can be stopped if the response criteria for stopping rules have been met. There are reports semiannually or more frequently or less frequently, as defined by the protocol, in terms of the individual monitoring plan that the protocol may have.

In Phase II we always monitor the first two patients plus at least--and the clever word here is "at least" ten percent of the total patients that are being accrued. It could be greater than ten percent. It depends obviously on the resources that you have available and the workload that the specific monitor may have but at a minimum ten percent of the patients on any Phase II study at any given time should be under active monitoring.

We don't do many Phase III studies at St. Jude but we do have a marching plan in the event that there is a Phase III study and it parallels the Phase II monitoring plan, with the exception that there may be other primary objectives in the Phase III trials that also require some monitoring.

St. Jude holds INDs or IDEs for a few products so under those circumstances, they could be Phase I or Phase II trials or whatever, but separately from those, if there is a particular IND or IDE for which St. Jude is the "sponsor" then there is a specific monitoring plan that is assigned to that study, and it will depend on the risk, what is known about the IND drug, what is known about the device, etc., etc., and may be more strict but at least it will be just like Phase I or Phase II studies I described to you before. Usually, under some circumstances like some novel therapy, it may be a little bit stricter in that the studies are being monitored a little bit more aggressively.

So, this is kind of in a nutshell how we kind of agree with the NCI in our data safety monitoring plan and how we would monitor our studies. Having said that, there is also auditing that occurs. So, there is a different auditing plan that I am going to give a lot of detail about, but for most auditing plans the monitors, once the study is done, will make sure that at least 20 percent of the patients have had a full audit of their records. But that is after the study is done

and that occurs over a long period of time. It is not as active as the actual monitoring which is occurring in real time.

I want to switch now and talk a little bit about the issue of adverse event reporting which has to do with monitoring and safety. We, at St. Jude, also have struggled with this issue and we struggle because there are a lot of problems in reporting. There tends to be a lot of over-reporting. That is, anticipated adverse events that are known in the investigator's brochure or known from other clinical trials are being reported on a continuous basis and that creates a big backlog of data that is important but not important in real time in terms of monitoring.

As you all know, there is increased research in new drugs and biologics. There is more oversight and scrutiny by federal agencies. Just like in many other places, we tend to get saturation effects. There comes a point where you see so many reports that it doesn't ring a bell; it doesn't ring any whistles or anything like that. So, we have to be careful that we don't over-report because then it gets us into the saturation effect and we don't react appropriately when there are red

flags that we should be paying attention to.

But one of the problems we have at St. Jude, which is very common for pediatric institutions, is that there are no denominators for how to make any sense of this; what constitutes a red flag? Where do you cut the line to say this is important or this is not important? There is no normative data for each of the populations that we have to deal with for Phase I studies, for Phase II studies and for the studies I mentioned to you. So, trying to approach this problem, we have tried to deal with this I think in a prospective way.

In terms of review, there are a lot of external events that we get from study sponsors. If there happens to be a drug that we are doing a study with but the drug is being used in adult studies or in other institutions, you know, the sponsors package a lot AEs and send them to you and we have to deal with those too. The problem with those is that sometimes the information is very sketchy and there is no opportunity for clarifications or for questions so that then you can put that in the context of your own experience with your own patients at your own institution.

The other thing is that the IRB is not a

DSMB. A DSMB has a very specific role; the IRB has to deal with a lot of other issues. They have to deal with adverse events and they should be looking at them and they should be judging them, but it is clearly in the context of the whole package of the research, whereas the DSMB has very specific roles and responsibilities.

The IRB is not the FDA who holds the IND file for the drug and knows everything. So, the IRB over here is getting little pieces of information and trying to make sense out of it in a more global sense. Then, the IRB also needs to rely on the local investigators to interpret the meaning of the adverse events that they are receiving from the outside, from the sponsors, because clearly the IRB doesn't have the expertise or the knowledge to put that in contextual features in terms of the study as it is being conducted at other institutions.

So, at St. Jude we decided to approach this problem first by doing quality improvement projects, trying to figure out where the problems were and where we could attach the problems. One of the first issues that we addressed is that at the beginning the PI or the research team needs to

report and categorize the events, but there was no systematic way of doing that. I mean, it was being done in paper form; there were different versions of that paper form.

One of the things that Don Workman and I recognized is that at least if at the beginning we could make this a standardized way and force everybody to do it the same way, then five, ten years later we actually would have a system in place that would provide a lot of the normative data that we would need in order then to do some process improvement.

So, the first thing that we did is to create this electronic submission that I will describe to you in a few minutes. This electronic submission is pretty neat I think, to use words of my nephew--it is pretty neat because it allows you then to disseminate that information very quickly to all the key players in the field and then they can do their own assessment the same time that the IRB is doing their assessment. So, the IRB will get a copy of this electronic adverse event and the IRB will do their own assessment of the adverse event and certainly give feedback and follow-up to the investigator. At the same time that it goes to

the IRB, it goes to our office of regulatory affairs which is also charged with making sure that agencies that have to be notified about these adverse events are also notified. So, it kind of takes the IRB and the investigator away from that responsibility of having do to that paperwork but it goes to a central office that then now deals with all the external agencies that have to look at this data.

Internally, it goes in a different direction. It goes to the vice president of clinical trials for internal reporting and internal processing so that the St. Jude DSMB or what we call our scientific review council which is called the CPSRMC, the clinical protocol scientific review monitoring committee, is really the scientific council which also has a function in terms of the cancer center doing monitoring. They also get a copy of the report and then they deal with it internally and then they can give also feedback to the principal investigator.

Don and I were very concerned with the first step in this process to try and make it uniform and to try to make it normative so that we could then create a system that, hopefully, would

help us in retrospect. So, we started this about 18 months ago. The first thing we did is we said let's create a form that is standardized. We can then make sure that people understand what is important in that form before we convert it into an electronic format. Then we were able, as we designed the form, to start thinking prospectively of how that same data could be captured electronically.

Then we developed a flow diagram as a quality improvement project of where this web-based report could go, which is a little bit of what I just showed you. We had to deal with some issues of security access and then we also had to deal with some issues of electronic signature that we eventually resolved.

One of the key features of this, which is a recurrent problem in adverse event reporting, is that there are databases and the databases don't talk to each other. So, one of the key features that we wanted to cover in this was to make sure that this adverse event electronic reporter was talking to the other databases in the hospital and was capturing information from the protocol office in terms of the protocol that the patient was

registered on and the additional protocols was that the patient was registered on because there could be some cross-talk between adverse events on different protocols or different PIs. I will show you an example at the end.

We also wanted to make this user friendly and make sure that anybody who is part of the research team could do this at any place in the hospital. Through a security pass they could access this web site and could potentially feed in the information in a very quick manner, without having to go to a dark office somewhere and grab papers and try to do it. So, there were some security access issues that got resolved but it was made available to anybody on the research team electronically.

We then tried to address the issue of internal reporting, that is studies in which adverse events are occurring in our patients at our institution versus the information of adverse events that are occurring at other sites that are being fed into our protocols in terms of the cooperative group studies, and so on and so forth. So, one of the things that we had to address is how we could link protocols so that the information

could be identified very easily. If a patient was registered on one protocol and the adverse event occurred on that protocol, we wanted to know what additional studies that patient was enrolled on so that when the IRB or the subcommittees reviewed this they could begin to get trends if there were complementary adverse events that were occurring from complementary studies and there could have been a red flag there that we needed to address.

In addition, we could share the information with the PIs of the other studies because they also have to be kept in the loop in terms of what is happening to patients that potentially may also be enrolled in their own studies concomitantly, for example therapeutic versus non-therapeutic studies.

Then, for external reports we wanted the investigators to help us sort that out because we couldn't sort it out. So, the investigators had to invest some time at the beginning sorting out external reports before they submitted them to us so that they would be more meaningful to us.

Then, the functional outcomes would be that there would be real-time reporting and that the IRB would acknowledge that through some

electronic time stamping mechanism. There are forced choices so that everybody has to do it the same way; no incomplete data submissions so we wouldn't have to address the issue of going back and asking for more clarification and more questions; easy access so it would be friendly; ability to generate single incident reports; ability to generate reports in a given time period. If you were noting a trend that something was occurring in a particular study over some period of time, you could capture that and, as you will see in the end, provide cumulative data that you could sort out to look at trends that potentially could be occurring. Quicker reporting times; ability for the IRB office to generate reports based on protocols; specific events across subjects, across protocols to give us some functionality at the IRB level to look at the data in different ways; generate internal denominators of trends that we wanted to look at; use standardized NCI toxicity tables for the oncology trials; and be able to record the IRB actions and updates from investigators onto previous reports. So, it wasn't a dead system. It was a system that the investigator could go back and add more information

or, when the IRB reviewed it, could add more information so it became a living document as the report was being done.

Let me give you an example of how this works. I couldn't get it electronically. It was going to cost me money to be able to do this electronically so I did some snapshots of what it looks like.

So, this page is accessible to anybody who is identified at St. Jude as a principal investigator or a member of a research team. So, if you are listed on the protocol as the nurse for that study, as the statistician for that study, as a pharmacist for that study, automatically you get access to this through a user ID and your own password. So, it is available to anybody who is part of the research team.

This is how you log in. Here I logged in and it says, "welcome, Victor Santana." Then it gives a listing of all the events that have accumulated during a particular period of time. It gives the event ID which is an internal working number. It gives the event date. It gives an identifier that I have erased here for a particular patient. It is usually a numerical number. If it

is an external event, then there is a way to code that to an external number. Sometimes you get an event from a sponsor and it is coded ABXY235, well, there is a way that you can code that the same way here so you can track it and use the same codifier if you ever have to go back to the data.

The status tells me, as an investigator, whether I have reviewed this or not. So, when I copied this the other day I only had one adverse event that I had yet to review that somebody sent to me for comment. Then, it tells me the date that the event was reviewed by me or that I modified it or I did anything to it.

Very quickly, it goes through a couple of screens that provide some general information. It tells you whether it is a St. Jude patient or not because if it is not, it throws you in a different direction in terms of the data that you need to capture because, clearly, the data is being captured for external adverse events a little bit differently than it is for internal. There is some information here in terms of the patient.

Then, it begins to do its own internal processing once it identifies the patient. It tells us, as you see at the top of the screen, all

the protocols that this patient is registered on. So, it goes back and talks to the data warehouse. If this patient is enrolled on ten studies, it will pull and identify all those ten studies. Then it will ask me, as the person putting in the information, under what study am I following this report. So, it identifies primarily the study and the adverse event, but it also tells me all the other studies the patient is on, and this is critical because this report will go to the PIs of all those other studies too. You will see it at the end for their comments. So, it provides a little bit of a cross-talk among studies.

Then, it clearly identifies the type of adverse event that is being reported. You have all seen this in different variations. For adverse events that require a CTC code it takes you to the CTC code so there is a link too so you don't have to scramble through 50 books looking for those codes but automatically it links you to those codes. Then, it allows you to put the descriptor, etc., etc. So, it is all being captured in a uniform language.

Then it goes to a page that allows the person who is submitting the information to do some

attribution on the adverse event. It is a click system but it reminds people, because we all tend to forget, what each one of those words means. So, it reminds me that I need to read when something is serious; when something is unexpected. It defines it very clearly because there are always a lot of questions from members of the research team what constitutes something that is unexpected versus expected. Well, there it is. It is, hopefully, black and white and then you select, based on your interpretation. It allows you to do one selection across lines horizontally for each one of those.

Then, there is a page that allows you to provide more information. One of the problems always with electronic information is that sometimes you can't capture everything in a unique format. So, there is a page that allows you to do a little more narrative form of how this all happened, and so on and so forth, so it can give you some additional data that you can comment on.

Then it asks you do you think, based on your interpretation of what has happened with the adverse event, that there is a follow-up that is needed. If you say there is a follow-up needed, then it links back to a reminder within 30 days

that you owe us a follow-up. The IRB reviews it and they also communicate directly. But if you think you have enough information and you want to submit a follow-up, within 30 days you will get a reminder that you owe us a follow-up.

Then it tells you something about what happened to the patient based on that adverse event. Then it asks the investigator or the research team to make some judgments based on the information that they have on that particular adverse event, and in terms of what they know is going on in the study does this alter the risk/benefit ratio for the other participants. Does this require modifications to the protocol or to the consent? And, does this provide additional information that we should be sharing with other people that are participating in the study? So, we ask the investigator to specifically address these issues with each adverse event.

This is an example of a summary page. All that data is generated in the end into a summary page. Obviously, I have whited out a lot of stuff. There is a doctor that is called "Dr. Teddy Bear." That is a famous doctor at St. Jude that we always use whenever we do electronic examples of things.

But it gives you a nice summary of who is doing this; who reported it; the protocol which was reported; the PI of that study; the date it was reported; when the adverse event started. It will list all the studies, based on that warehouse capture of data, that the patient was on. It will quickly generate all that data into specifically designated toxicities that were reported as part of the adverse event. The attribution and nature that you selected gets summarized; additional medical history; treatment prognosis; patient outcome.

Then it tells us at the end--this all goes to the IRB--it tells us at the end how the principal investigator judged this in terms of his own interpretation, that it doesn't alter the risk/benefit ratio; does not require modification, and so on and so forth.

So, it goes electronically--only focusing on the IRB part of this, it goes electronically to the IRB and there is a designated person in the IRB office who will certify that he or she has received this report, and will certify it electronically down here with the date. Then it allows, at the end, to add additional information when the IRB actually reviewed it. So, the IRB will come back

at the end of the meeting and put in there the date that it was reviewed by the IRB so it provides a tracking record of when the IRB looked at it.

Another very neat thing I think, and I like to use that word, with this project was that it allowed cross-communication among investigators. In that example I gave you, the message that there was an adverse event reported in August, '99 will also go to all these other studies that that patient was enrolled on. So, the PI of the SD/01 protocol will also get the message and will get the summary report, and the PI of that study has to pay attention to that report and then make a decision whether he or she thinks it may or may not be related to his study too because there could be complementary toxicities and they are the only ones who are going to know that, not the IRB unless it gets reported through a different mechanism.

So, it forces all the PIs of all the studies that the patient is enrolled on to also critically review the adverse event and make some judgment about whether it is related or not related to their own research. If it is, then it takes them back to make some comments to the original report that I submitted on my study. So, there is

a page that allows the other PIs to come back in and give additional information.

This doesn't project very well and I apologize, but all this data then can be captured in different ways. In this particular page there is data on one study and all the adverse events that have been reported on that study within, I think, a six-month period. Each one of those cells can be manipulated to provide you different ways of looking at the data. So, you could ask the data to be cut only at grade 3 or grade 4 or only deaths on that particular study. You can ask the system to report all deaths on all patients across three studies to see if there are complementary problems, and things like that.

So, this is where we are right now. We established this about 18 months ago. The next phase of this project is actually now beginning to mine the data so that we can create some normative rules of when we should be setting lines that raise red flags that we should pay more attention to. So, I think that is the strength of this, that now it unifies it in a certain way so that now we can go back and make some sense of all the data, and I think with that I will stop. Thank you.

Oh, obviously I didn't thank everybody that was part of the team. Don Workman, our IRB administrator, was very involved with this. Donna Hogan, from the IRB office, is in charge of the AE reporter. Then, two individuals from clinical informatics were the ones who put all these ideas to work. Thanks.

Now I think we have some time for questions before we go into the discussion.

Committee Discussion

DR. HIRSCHFELD: I have a question for Dr. Anderson. Dr. Santana discussed the goal of the project at St. Jude to get some normative data on what types of events one can expect and, perhaps by implication, what needs to be monitored and what doesn't need to be monitored, and when things do occur how serious they are. Does the NCI have such a program? If it does, are there any analyses that you are able to share? Or Dr. Smith could answer the question.

DR. ANDERSON: I am not aware of a specific program for pediatric oncology, you know, with the AdEERS system for bringing in information. There is data trial by trial, especially for IND agents. That sort of information is accumulated.

But to provide sort of a baseline level of here is what to look for over time, I don't know that that is a specific project that is under way right now.

DR. SANTANA: Yes, in fairness to the question, we are not doing that right now. We have the capability based on this project after we have been into it 18 months because we thought about that when we tried to build the electronic format. We now have the ability to do that but, in fairness to the question, we have not done that. We are just establishing the data and, hopefully, at some point we will begin to analyze it once we have enough data to make some sense out of it. We are really only, particularly right now, focusing on the St. Jude studies, studies where we are the primary sponsor.

DR. SMITH: Steve, as Barry said, we do have the AdEERS system that is an electronic reporting system. So, you know, there is the capability if there is a question about cardiac toxicity or other organ toxicity to pull up all of those reports for a particular toxicity. But in terms of what to look for, you know, if the question is what toxicities are occurring in what types of trials, then the Phase I and Phase II

databases of the Phase I Consortium and the Pediatric Brain Tumor Consortium are more relevant because if the AE reporting is being done correctly, then it is the unexpected events. You know, what you would really be interested in is the whole universe of events and, as well, the denominator of how many patients were in those trials. So, I think I would approach one of the consortia for early phase trials or COG for later phase trials if the question was what type of events are occurring, how frequently they are occurring, etc.

DR. SANTANA: Dr. Przepiorka?

DR. PRZEPIORKA: Back to Steve, if I could turn the question right back to you, does the FDA have enough information or a database on SAEs in pediatric trials to actually do that same study?

DR. HIRSCHFELD: Short answer? No. We would like to but we don't have a database that captures premarketing adverse events. We only have a database for postmarketing adverse events. That is mined in a fairly rigorous and maybe even imaginative way to look at frequencies of what one can expect but, again, it hasn't been examined sufficiently on the basis of pediatrics and, even

more specifically, on pediatric oncology. So, we don't have the data and that is one of the issues and one of the reasons for having this discussion this morning.

DR. DAGHER: Dr. Santana, another question about your presentation which also may impact on the NCI perspective, one of the challenges you identified was the situation where a patient is enrolled on several studies at the same time. I am curious to know how often that happens and whether that is somewhat unique to St. Jude, or is that something that you also see across pediatric studies that NCI supports?

DR. SANTANA: The way the system is designed is that it will pick any protocol that the patient is still currently enrolled on. It doesn't mean the patient is on active therapy on those other studies; it may be that they are in follow-up for those other studies for example but the patient has not been taken off those additional studies. We did that on purpose in terms of thinking outside the box, that if there were long-term issues with patients that had been enrolled on other studies and then you began to see trends that were complementary to a group of studies that together

created something in the future, we could go back and capture that.

So, your point is well taken. The primary study that is generating the adverse events is many times the active study that the patient is being treated on. But we also wanted to make sure that we were able to capture data on studies where the patient was not actively receiving therapy but was still technically enrolled on that study.

Having said that, we also wanted to capture non-therapeutic trials so it will list any trial. It won't make any distinction whether it is therapeutic or non-therapeutic up front.

DR. DAGHER: Supportive care--

DR. SANTANA: Yes. On the last page there was one trial which was a behavioral medicine trial on which the patient had been enrolled that had nothing to do with the primary therapeutic trial, and that showed up too.

DR. HIRSCHFELD: May I ask for just one more clarification on your presentation, Dr. Santana? You said that the system in use at St. Jude will bring up the relevant definitions for a serious adverse event, unexpected, etc. What is the source of those definitions? There are several

places that are source documents, including ICH documents.

DR. SANTANA: I think what we did was an amalgam of the different definitions and tried to make it into a definition that people could understand without having to pick up a dictionary or call the IRB administrator. So, it was really looking at all those documents and coming up with some definitions that were kind of a semi-practical way that people could relate to and then choose the right box. Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I have a suggestion for future meetings on this subject, and that is to invite a representative from the pharmaceutical industry to make a presentation because although you might argue that the FDA knows very well how the pharmaceutical industry functions in terms of monitoring adverse event reporting, on the other hand, others around this table and others participating in the Webcast or viewing the tapes later on might not. The fact is that there is extensive experience with clinical trial monitoring in the pharmaceutical industry and, likewise, with adverse event reporting. Although I see a great parallel and even consistency in terms of the

procedures and methods that are used in your institution representing an academic experience, and at the NCI particularly with the cooperative groups, there are some points that are different and that would merit discussing and presenting because they might present opportunities for improvement.

DR. SANTANA: Are you in a position to highlight some of those points?

DR. GRILLO-LOPEZ: Well, one thing that just came up in the discussion was the subject of denominators. Certainly, when you are conducting research with a new therapeutic agent the database at that pharmaceutical company contains the most information regarding the safety experience with that agent at any given point in time. Of course, all of that database is transferred to the FDA as required. But investigators participating in multicenter trials could certainly call the project clinician who would have access, through his biometrics group, to that database and would be able to provide information about what the experience has been with other events of that nature.

DR. HIRSCHFELD: Dr. Santana, if I may

just respond to the initial suggestion, and I want to thank Dr. Grillo-Lopez, one of the reasons you are at the table is to provide that. Previously at the meetings of this committee we had multiple representatives from the pharmaceutical industry and had routinely asked for presentations but there was a policy decision made outside the group that you see here today to restrict that. So, since you are new to the process--had you been involved earlier you would have seen what you are suggesting--maybe you can help us restore that previous mode of interaction because we found it helpful also.

DR. GRILLO-LOPEZ: Yes, that was an unfortunate decision and I, of course, didn't know about that. I think it is a three-legged stool or a triangle, as you were saying, with the participation, on the one hand, of the NCI and cooperative groups particularly, individual academic institutions and the pharmaceutical industry as sponsors in conducting research. We should not forget that third leg of the stool because a lot of the research that is conducted with new agents particularly is sponsored by the pharmaceutical industry and the pharmaceutical

industry holds the databases for the results of that research, and one particular institution may have had a lot of experience with a new agent but not necessarily all of the experience because many other institutions might be participating and they may not be communicating between themselves but certainly the database of the pharmaceutical company holds all of that information.

DR. SANTANA: Dr. Adamson?

DR. ADAMSON: A couple of comments, first, I want people to be aware that what Dr. Santana presented, which I think is something academic institutions should strive for, is not the norm. Most institutions are many steps behind what St. Jude has done and is capable of doing, and in most institutions what you are looking at are piles and piles of paper. So, your colleagues are to be commended on beginning to address what is a problem for all academic institutions.

I wanted to comment that I think the current SAE and AE mechanism--and this will echo and build upon what Victor said--has some significant flaws. I mean, we can be inundated with reports that we cannot interpret, and what I would say is that the large majority of external

reports, when it comes to the cover letter, "because of regulation blah, blah, blah, you are required to submit this to your IRB"--the large majority of those reports, as a member of an IRB as well as an investigator, one cannot interpret. It gets down to knowing the denominator and you said there are large databases but the problem is you need real-time access to that database in order to interpret it. There is too large a line of these reports coming in for the investigator to call and track down every report--is this relevant? Has the risk/benefit ratio really changed for my patient?

Rick said earlier we should try to focus on pediatrics so I will. As one moves forward--because this is the problem and it is not limited to pediatrics but is a problem across the board that one can't interpret the large majority of these reports and we are fooling ourselves if we think simply by submitting the document to the IRB you have fulfilled your obligation. That is not improving patient safety. You may have fulfilled the regulatory obligation but you have done nothing to improve patient safety. We need access to the type of data you referred to that industry has to interpret this.

To focus on pediatrics, I will give you an example. We did an industry-sponsored study and there were many studies of this investigational agent. The large majority of reports were about myocardial infarction in a 76 year-old. That is important but it is not particularly relevant to the pediatric population. So, when we move forward and ask for data, I think we need to have some depth to that data, that is, not only the frequency of the event but somehow to categorize what population that event is occurring in. Because if an event is occurring in a 30 year-old--and my mark of what I think is young is continually shifting upwards--

[Laughter]

--but if an event were to occur in a 30 year-old you might spend a little more time looking at that event as far as, you know, was it a cardiovascular event relative to someone who is more elderly. So, I would hope that one looks at the regulations and makes it that you don't just send the report, but the report has to be in context and the context is what is happening globally with the safety of this drug, focusing on its particular toxicity, but within that have the

depth to say this is the breakdown of the population that we are looking at. I mean, you don't need to get it down to all 12 year-olds, all 13 year-olds or all 20 year-olds but give us some sense of what is happening. Otherwise, I don't think we are doing anything for patient safety in a meaningful way for the large majority of these reports.

DR. KODISH: This is Eric, in Cleveland. I hope my timing is okay and you can hear me.

DR. SANTANA: Yes, Eric, go ahead.

DR. KODISH: Thanks. I want to add an idea to Peter's idea which I think is very important and relates to the point I was trying to make about regulation actually harming patient safety on some level.

A 76 year-old who has a myocardial infarction on a drug that we are testing in a pediatric population compared to a 30 year-old compared to a 20 year-old I think gives us the ability to maybe, rather than contextualize which would be great--ut maybe a more simple idea is to provide some sort of sorting function so that we are not just, for regulatory or prevention of litigation, trying to download all of these reports

to our IRBs to say that we have fulfilled regulatory requirements, but that at some level there could be a sorting function so that the events that are going to be relevant to children are presorted, if you will, and not disseminated across the country automatically. I think we do need to be concerned about the paradoxical effect of everyone feeling that because we have filed all these adverse event reports that everything is going to be okay.

DR. SANTANA: Eric, just to play devil's advocate with your comment and Peter's comment, who defines what is relevant to our population? It is us. And, I think that is probably why we are here today. We have to define in our studies, either prospectively when the study is being created based on what we know about the agent or whatever is going to happen in the study or during the conduct of the study as we review things--we are the ones that have to define what triggers that it is a pediatric issue that we need to address. If not, then we just rely on these big data warehouses that have data that are not relevant, but we have to define the relevance up front or during the conduct of the study.

DR. KODISH: I agree with that and I think that maybe the discussion could focus on how we sort those that are and those that aren't, maybe starting with something as simple as an age cut-off.

DR. SANTANA: Well, one of the things that Barry mentioned in his presentation, and in retrospect I wish he had given more discussion to his point, was this issue of how some of the consortia--and it is the PBTC Phase I group or maybe it is the COG--that those committees electronically and telephonically and through computers meet on a regular basis and they review real-time data of those patients that are on Phase I studies. I presume, and I think correctly so, that there also is, as part of that review, the toxicity and the adverse events occurring in those patients. So, that whole arm of this process, which we didn't discuss in great detail, I think is very strong because it relies in part on the research team to very actively monitor this in their own hands.

We have to have checks and balances through other groups too but the beauty of that is that it allows the research team who is actually

conducting the research in real time to be able to communicate and evaluate these and then prospectively, even as the study is being conducted, define what are the parameters that trigger the normative data that we are looking for because in reality it is an experiment. Until we do it we are really not going to know the whole scope of things that may happen. We kind of can predict based on what are the things that may happen or what are the things that would really worry us. Right? If somebody dies we all worry, or if something unexpected occurs we all worry. But for the majority of things, things are happening and it creates a lot of noise. I agree with you, Peter, it creates a lot of noise. So, I think we have to go back to the research team and address what their role and responsibility is to help us at the other end figure out how this data may be interpreted or may be incorporated.

DR. ADAMSON: I think you are right. Phase I, in many respects, is somewhat easier because the data is being monitored in real time and the numbers are small. I think it is a multi-level process. It begins with the treating institution and the team at that institution

recognizing and identifying the event and reporting it to the study principal investigator.

What we do in our consortium is once it is to the study investigator it immediately comes to us and then on a weekly basis all the events on every study are reviewed. What we have the ability to do and what we focus on is that we don't just look at the serious ones because the serious ones are usually pretty straightforward. We look at the non-serious toxicities to look for trends because we are doing a dose escalation and so we want to know. Okay, we are starting to see some grade 2s in an area that wasn't described that are not triggering any alarms but, in fact, maybe we need to do more careful monitoring of hepatic function because we are seeing a lower level of toxicity. So, it is a multi-level review but we have the ability to look at all the toxicities on a study as a function of dose, as a function of severity and that gives us the context to interpret it.

DR. SANTANA: Dr. Grillo and then Dr. Carome.

DR. GRILLO-LOPEZ: I find that we are talking about adverse events in general but also about serious adverse events and perhaps not always

making a distinction about the different reporting requirements for those. Certainly, in the pharmaceutical industry we collect each and every adverse event but the reporting requirements are different if it is a serious adverse event. It might help if someone from the FDA would just summarize what the requirements are for reporting to an IRB and reporting to the FDA.

DR. HIRSCHFELD: The definitions are essentially ICH definitions, International Conference on Harmonization, that the FDA adopts. The requirement essentially is if it is serious an unexpected according to both triggers, then there has to be what is called a rapid report filed. That can be filed by a number of mechanisms. The time frame typically is within 15 days and sometimes, depending on the circumstance, can be 7 days. But that is still not what could be called real time. It is essentially informing. All other adverse events do not have to be reported to the FDA, other than in the annual reports which are required. The annual reports are due within 90 days of the initial filing of the IND.

DR. GRILLO-LOPEZ: How about to IRBs?

DR. HIRSCHFELD: The IRB requirements work

on multiple levels. So, the IRB can set their own policy but in the FDA regulations, in 21 CFR 50, the reporting requirements for IRBs parallel those of reporting to the FDA.

DR. GRILLO-LOPEZ: If I may, in that vein I would make the point that we have to be very precise, very specific and very timely in reporting serious an unexpected adverse events. At the other extreme, there is a multitude of minor events that are still adverse events and need to be in the database at some point without creating this backlog, this bureaucratic mass of paper and electronic data coming at you without denominators, which doesn't make much sense at any one given point in time for one patient.

However, many times we find at the end of the development of a new therapeutic that when we have to put together the documentation to submit to the FDA, one of the things that we, in industry, have to do is to do an analysis across all of the experience with that agent, Phase I, II, III, all of the studies ever done, which is called the integrated summary of safety. Many times it is only then that certain trends become significant that were not significant earlier on when you only

had the Phase I or the Phase II experience. That is why it is important to report each and every adverse event but not necessarily make it a bureaucratic jungle where you just get so entangled in paper and data that it doesn't make sense at any one given point in time.

DR. SANTANA: Dr. Grillo, you represent the pharmaceutical aspects of this. As somebody from that group specifically focusing on pediatric oncology issues, how would you advise your group of things that we need to have access to, and in what time lines would you advise your group that we need to have access to those data so that we can complement that with what we want to do?

DR. GRILLO-LOPEZ: I may not be the right person to respond to that question because I am an adult oncologist, not pediatric oncologist. In fact, in over 20 years in industry, I never did a pediatric study, ever. So, I have zero experience and I have to be the first one to admit to that, other than my rotation through pediatric oncology when I was a fellow.

But I think there is a variety of ways and systems and procedures that the pharmaceutical industry utilizes to follow-up, collect and be able

to analyze adverse events. It begins with the case report forms coming in from the different sites participating in a multicenter study. I can tell you that for all of the studies that I was ever related with, I would personally look at each and every piece of paper coming in from the different sites, or the safety officer responsible within my group would do that even before it went into the database. So, if there was a major red flag that was apparent even just from the experience in one patient, we would see that. Of course, immediately that was entered into the database and periodically we would print out tabulations that would indicate if there was any trend that was becoming obvious.

So, there is a variety of checks and balances that are in place within the pharmaceutical industry to follow-up on these issues. Again, I would suggest that investigators who are participating in multicenter pharmaceutical industry sponsored studies, that their point of access or one point of access might be the project clinician within the pharmaceutical company who is the person responsible and/or the safety officer within that company when issues arise or questions arise regarding a specific adverse event.

DR. SANTANA: Dr. Carome?

DR. CAROME: I will just note a couple of things. I think it is important for this subcommittee to be aware that this discussion is occurring elsewhere. The Secretary's Advisory Committee on Human Research Protections had a panel on adverse event reporting and they are going to continue that discussion at their next meeting. They had a panel in December and they are going to continue the discussion in their March meeting, coming up in a couple of weeks. And the discussion is exactly the same. I mean, the types of comments being articulated are verbatim what you hear repeatedly.

I think the Department recognizes that there is a need to make adverse event reporting more meaningful and less burdensome in order to better protect human subjects, and there are ongoing discussions between our office, the FDA, NIH and other federal departments and agencies on how best to do that. So, it is recognized to be a problem and developing strategies is complex but we believe important.

If you look at our regulations, just the HHS regulations CFR 46, there is no adverse event

reporting requirement. There is a requirement for reporting what are called unanticipated problems involving risk to others. It is our view that most adverse events that occur in clinical trials do not fall into that category and, therefore, under our regulations the vast majority of adverse event reports do not need to be reported under our regulations. Those that we particularly care about, and we have articulated this at the Secretary's advisory committee in December, are those that represent unexpected, serious harms to subjects, which are words that come from another part of our regulation. Those are the types of events we think should get to IRBs and that we care most about.

DR. SANTANA: So, Mike, where do you think the confusion comes that all these reports are being generated and submitted to IRBs? Where do you think the communication breakdown is in terms of what the regulatory agencies want versus what the sponsors or we, as investigators, see that you guys want and need to comply with?

DR. CAROME: There are probably multiple reasons. It is clear to us, and I think to others, that the greatest burden comes from these external

adverse events that don't occur at your site but, because we do research at multiple sites, the sponsors deliver those reports or ask that they be delivered to the investigators at all sites. So, now we have 100 IRBs maybe receiving the same event so it is those external events that are being multiplied to multiple IRBs where the burden has been articulated to us as being most severe, and if the letter reads that under the regulations you must deliver these to your IRB, that is certainly one source. It is not our regulations that are demanding that and I would posit that a close look at the FDA regulations probably doesn't justify all those events going to the IRB as well. But FDA would have to comment on that. So, that is one.

I think it is driven by fears of litigation liability. You know, who makes this initial assessment about unexpected and serious? We think that at one level the sponsor and the investigator can be doing that. There are some who think those are conflicted parties and maybe we need an independent body making those decisions so people are driven to having an independent body be the IRB looking at them. So, I think there are multiple reasons. Those are a couple that I would

highlight as perhaps driving it.

DR. SANTANA: Rick, do you want to comment on the FDA?

DR. PAZDUR: Well, I just want to comment in general. Could there be attempts to try to give investigators more guidance on specifically what needs to be reported? I think there is a tendency to report a lot to cover oneself because we don't have good guidance on exactly what those words mean. Maybe we need to look into that. You know, if you go over your phrase that you gave, there is a lot of interpretation here and somebody could say that it might be the index case; they are not even sure of the attribution issue, and I wonder if we really need to give more guidance to perhaps cut down on some of this. I don't know, do you want to comment on that?

DR. CAROME: I think for us, we believe guidance is essential and it is the most important step. We have had discussions with FDA. We are prepared to draft guidance that articulates in more detail what I just articulated to you and I previously articulated at the Secretary's Advisory Committee on Human Research Protections in December. But we think, yes, guidance is the

important step. We think because adverse events are primarily referenced in FDA regulations the guidance needs to come out of both of our offices or entities.

DR. SANTANA: Dr. Smith, I think you had your hand up?

DR. SMITH: One point, and, Victor, I think you made it, there is over-reporting of adverse events, expedited adverse events, despite FDA's stated requirements, despite their statements in protocols of what does require expedited reporting. So, I think one of the initiatives that we want to undertake in the next few months is an educational initiative to try to limit the over-reporting of things that, in fact, just do not require regulatory reporting. So, this will decrease some of the burden at the institutional level.

It doesn't address the issue, however, that Peter raised about when you get a letter from a company saying that this event occurred. I wonder if there is a role for the Phase I Consortium itself or the COG itself to play the filter role that Eric Kodish was talking about in terms of saying we have reviewed this, and our

recommendation to IRBs, when they look at it, is to say this isn't applicable for pediatrics.

DR. ADAMSON: We are actually now doing that, Malcolm, when it comes, you know, a COG trial. When we disseminate it we usually give a recommendation that, in our view, this does not change risk/benefit or, in our view, it does change the risk/benefit ratio and it should be reported. So, we try to put it into context but, of course, every investigator has the ability to interpret the data and make their own decisions.

DR. SANTANA: Dr. Przepiorka, you had your hand up?

DR. PRZEPIORKA: Yes, I clearly remember sitting through multiple discussions at the initiation site visits with sponsors regarding the definition of an SAE, and I recall a few years ago, after the incident at Penn and the FDA sent that Webcast to all the academic institutions with a long, drawn-out discussion on what is an SAE, and I sat here and I think we listed them, although I didn't see them on any of the slides this morning. I won't go through them but I don't see any that is very specific to pediatrics and I am wondering if there is any SAE that should be added to the list

specifically for pediatric groups. I am thinking about long-term cognitive dysfunction or something like that.

DR. SANTANA: Ruth?

MS. HOFFMAN: I was just going to mention that I sit on the IRB at Children's National Medical Center, as well as the DSMB board there, and from a lay perspective it is very difficult to get lay people to continue with the responsibility because of the burden of time commitment. There is no monetary compensation. I don't get paid and I am not an employee of Children's National Medical Center. I spend three days a month totally related to IRB-related work between the protocols and the SAEs and AEs. I mean, it is just a stack of paper and usually the check-off is that the AE has nothing to do with the protocol at all and, you know, maybe you can eliminate that whole column and, again, reduce the workload. But, I mean, they have a very hard time to even recruit members from the community and that is a requirement of the HHS, to have a lay person on the committee. So, the guidance document would be great. It would certainly help from our perspective as well.

DR. SANTANA: Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I would suggest that further guidance is not necessary, that what we need is education. The guidance that is already provided by the FDA is very specific and very clear as to what is a serious and unexpected adverse event, and what we need is for those involved in research, and particularly at the IRB level, to have an understanding of what that means. I think it is education. Generating one more document to file away does not help anyone.

DR. SANTANA: Peter?

DR. ADAMSON: I agree that the FDA guidance on the definition of an SAE is clear. What I think the point is, is that it is not particularly functional in that it is generating an incredible amount of paperwork for institutions. What we get are, indeed, SAEs by the definition. That information I don't think is improving patient safety and that is why I would actually agree that we need to re-look at what we are requiring to be reported to IRBs across the country because it is not only a multi-institutional trial, it is when you have multiple trials of an investigational drug that affects all those trials.

DR. SANTANA: Dr. Keegan?

DR. KEEGAN: Yes, I was wondering if we could go back to the concept that was discussed before about having a central body that looks at all the adverse events because, as you say, every individual institution is going to be unable to look at a single adverse event out of context with the rest of the data. So, to what extent are there really plans in place to have a central point that has all the data that could make reasonable interpretations that have people with the background information who could interpret the adverse event information in the context of animal and nonclinical studies and other things to make relevant decisions? Because you mentioned that in the instance of the consortium but it doesn't seem that that is a general theme. To some extent, I don't think any one individual is ever going to be able to make a conclusion on the index case but we certainly can't ignore the index cases because that also puts patients at risk.

DR. SANTANA: Patricia, in follow-up to that comment, what kind of body were you thinking of? What ideal body, if you had to come up with that, would you propose?

DR. KEEGAN: Well, it sounds like that is

sort of the model that the consortia are working on and I thought maybe there could be more discussion of whether it could be that sort of model, where the consortium looks at adverse events and then sends out their interpretation as a central repository analysis, much like a medical monitor would do at a drug company to perform that same function.

DR. ADAMSON: Well, I think it is easier for smaller studies, and the key thing is you have access to all the data. So, when we do an NCI-sponsored study where the NCI is cross-filed there is a drug monitor at the NCI that has access to all the data and, in fact--correct me if I am wrong, Barry--usually when an AE comes out there also is a recommendation of an interpretation when it happens. I can't say that is the case uniformly for industry-sponsored trials. But the multiplying effect I think is a difficult effect for when events are occurring really that are distantly related to the study that you are doing.

DR. SANTANA: I think the advantage that we have in pediatric oncology is that it is a smaller universe and most pediatric, if not all pediatric oncology studies are really conducted in

the list that Barry showed, plus a few others. Right? So, we are a much smaller universe so that if we adopted a model similar to what is happening in the Phase I consortium and expanded that to all the participants in those groups because it is a small universe, we could at least set that model and see if it works for us. Because that is what we are really here for, right? For pediatric oncology, not to ignore or belittle the other important issues that are occurring with adults but we have that advantage and maybe we should think of that model as a test case for reviewing adverse event reports to make it more functional and timely.

To me, the issue is time. So, what if something happened six months ago? It doesn't help my patient who is on the study now. Right? So, maybe we have that advantage. We are a small group. Malcolm?

DR. SMITH: The other possibility is, Pat, we are at the earliest stages of setting up a pediatric central IRB and so, you know, could that be a body that is somehow constituted so that it could play that role nationwide and then other IRBs could use that information if they chose to?

DR. SANTANA: Since you raised the issue I am going to try to explore it a little bit further. There has been some recent discussion I think in some of the things I have been reading about whether DSMB should play some of this role. Do you want to comment on that?

DR. PAZDUR: I would just say that I had a side conversation with Susan, here, and one of the issues is that usually DSMBs are single trials. Now, would one consider, for example, kind of a super-DSMB not for the trial but for the drug that is being investigated by a commercial sponsor? Could a commercial sponsor, for example, if they are investigating drug X in, you know, 50 diseases in pediatrics, in geriatrics, and whatever, to have a coordinating center to look at this and then issue some type of report on these individual toxicities?

Again, I understand exactly where Peter is coming from and the comments, having been there. You know, you get all this morass of information which is almost useless because nobody knows what to do about it and we are just generating paperwork with a pretense basically that we are doing something to further not only children but also

adult clinical trials.

Here again, you know, although we are talking about pediatrics, this does have obviously ramifications for adult medicine and adult clinical trials. Although we may want to kind of say, well, some of the adult toxicities may not protect for what may go on into childhood toxicity, again, that is another level of clinical judgment and subjectivity that comes into play here. Many of these drugs, especially with the IRBs, are not solely being looked at in children. In many of your hospitals, since you practice exclusively in children's hospitals, that may be the case and your interest may be in that group, but for a garden variety IRB at a university hospital they may have ongoing studies in adults with breast cancer, colon cancer and pediatrics. So, they need to look at this so it isn't that helpful sometimes to the larger IRBs, the university IRBs.

DR. SANTANA: Dr. Reynolds, you had a comment?

DR. REYNOLDS: I wanted to make it clear that the DSMB process is a little different in the pediatric setting. You have one for your consortia, don't you, that look at all the studies

that are going on and that are not specific to a drug. But I think taking that in the context of what we are hearing from Ruth, and I hear this continually from a lot of people, the burden that is placed on the IRBs at the institutional level is substantial.

Just taking a round number of 20 institutions in your consortia, Peter, you have 20 different IRBs looking at each one of these adverse events. How many people are on each of those IRBs? Certainly, the total number far exceeds the number of patients on a study by an order of magnitude or two. So, it is that process, yet we have a centralized DSMB process. So the real central issue though comes down to the responsibility that the IRBs have under the regulations to be the ultimate and final arbitrator of whether or not this is going to be safe and appropriate for the patients in their institution.

Somehow we need to use the word that I first learned in the context of Steve Hirschfeld, "harmonization." I see it over and over again with the regulations you are harmonizing. I think we need to somehow harmonize this process so that we can then decrease the workload for these poor

people in the IRBs that, as you have heard, are volunteering their time and they are a precious resource that we could exhaust and then we wouldn't have anymore volunteers.

DR. SANTANA: I want to follow-up on a comment related to the previous issue of whether there should be another body that could help us review these things and probably give better knowledge to practicing oncologists. You know, one of the concerns I always have about creating another body is that you don't destroy mass; it doesn't go away; you are just shifting it to another group. If we do that, I think we run the same risk without clear guidance of what that group needs to be doing. They are going to be getting the same paperwork we are getting now. So, unless there is guidance at the first step, which is let's clearly define what we should be looking at and streamline that, it doesn't really matter where it goes to, whether it goes to an IRB, to a DSMB or to another group or another consortium.

I think that may solve part of the problem but it is really shifting a little bit of the responsibility and what I want to get at is that we should probably encourage ourselves more to define

the responsibility and the process rather than creating another group. That is just a general comment. It is not meant to be a criticism. It is just something we need to think about.

DR. KEEGAN: Actually, going towards that--what you say, it doesn't help to create another group that is duplicating effort so it would only be effective if, in fact, the other groups then would agree to accept the information provided by the central group. So, I think that has been the issue with central IRBs all along. While IRBs are crying out that they are overwhelmed, yet, they also refuse to defer that part of their responsibility to another group or to a central IRB. Do you think that for a central pediatric IRB there is more willingness to do that, Malcolm? I mean, are they willing to say, okay, we will allow somebody who is going to make an integrated analysis to do that and we will accept their judgment?

DR. SMITH: It will vary by institution. You know, the adult IRB has a facilitated review process and when a local IRB accepts the central IRB as the IRB of record, then the central IRB is responsible for the review of the adverse events

relevant to that study. In pediatrics, based on a survey that the Children's Oncology Group did, there is a high level of interest in a central pediatric IRB, both among PIs as well as among IRB chairs. But when it comes to implementation, some institutions will accept it wholeheartedly and some won't. But those who do will certainly be saving in terms of the effort expended on this.

DR. SANTANA: Peter, one last question.

DR. ADAMSON: I just wanted to follow-up on that. So, it is not only the IRBs who are sometimes unwilling to give up the ability, it is the institution. The institution more often than not will actually tell the IRB, you know what, we need an independent IRB; we are not going to accept it. So, they may even take it out of the hands of the IRB as far as whether they are willing to or not. So, IRBs are looking for ways to cut down their own work but it is not always coming to them.

DR. SANTANA: With that final comment--Ramzi, I will defer to you.

DR. DAGHER: Just very briefly, you seem to have identified a sense of challenges in terms of the filtering. One is how to decide how relevant an adverse event is, and that is not

really just specific to pediatric oncology or oncology, for that matter. The second one, which Peter Adamson was trying to focus on, is how do you filter out the adult oncology experience or other experience that is submitted to you in terms of how relevant that is or isn't to the pediatric oncology setting.

Now, you mentioned age and the nature of the adverse event. Those are two potential criteria. I am curious to know, and probably we will get into this more in answering the questions from Peter Adamson, Victor or others who have dealt with this, what criteria do you use in making decisions about filtering the adult oncology reported events and deciding how relevant they are to your specific studies?

DR. SANTANA: I think with that question we will go ahead and try to address the questions for the committee because I think we will cover that.

DR. PRZEPIORKA: Can I just ask one more question?

DR. SANTANA: Yes, Donna?

DR. PRZEPIORKA: You had indicated that, if I recall, your institution does not take

patients off protocol so that you get long-term follow-up. I was wondering if you thought that was appropriate for everybody to be doing in the pediatric population or if there is some time limit, like by age 35 we are not going to look anymore, or something like that?

DR. SANTANA: Well, if we are conducting active research on those patients, those patients would come off their primary therapeutic protocol and get enrolled on a non-therapeutic protocol, which is an umbrella protocol we have for long-term follow-up. So, they would still be research participants and we are collecting data on long-term effects, survival and things like that. So, the patient would come off the primary therapeutic protocol once they are transitioned into the long-term follow-up protocol on which research is being conducted. So, those active protocols will not show up in the reporter but the long-term follow-up will show up in the reporter for that patient.

Questions for Discussion

Let's go ahead and try to address the questions that we have before us. Just for the purpose of the minutes and the documents, I will go

ahead and read the questions to the committee, the introduction, and then we will take one question at a time.

The tolerance for risk in cancer therapeutics is different than for most other medical therapies. It is also recognized that children are a particularly vulnerable population and regulations and procedures have been implemented to provide protection to children participating in clinical research. The following questions relate to the setting of children with cancer participating in clinical trials.

Under the heading of "principles" the question is, what are the principles that should be addressed in safety monitoring of clinical studies that enroll children with cancer? If the principles are adequately stated in existing documents, statutes or regulations, please identify the relevant documents and sections.

Barry or Malcolm, from the NCI perspective, do you have any comments on existing regulations or documents that we could reference to?

DR. ANDERSON: In terms of the DSMBs, the composition of DSMBs, that sort of information is

provided in OHRP. In terms of the frequency of monitoring and the exact nature of the monitoring, what is monitored which is part of the discussion we had, I don't know that that is laid out as clearly. We have guidelines that we work with at CTEP and NCI but I don't know that that is in regulatory form at all.

DR. SMITH: Yes, there is the overall policy on data monitoring. That is really not very prescriptive in terms of here is what you have to review; here is how often you have to look at it; and here is, you know, who should be looking at it. It says you need to have a plan but it is not very prescriptive in terms of what the plan is. Each of the institutions has their own data and safety monitoring plans, particularly for Phase III trials, and those tend to be more prescriptive and detailed in terms of what is happening. But in terms of early phase trials, you know, I am not aware of kind of NIH-generated documents that provide detail about what, how, when and where this needs to be done.

DR. SANTANA: Go ahead, Barry.

DR. ANDERSON: And having been on the panel of people who looked at the cancer center

data and safety monitoring plans that they had to submit, previously I think a lot of people would recognize that for early phase studies it was the investigator and their research nurse that looked over the data with the most frequency. A lot of times I think there was not a lot of oversight from outside of that small group. It was clear from looking at the different cancer centers that there is a huge spectrum of what in reality they were doing and when you told them, you know, you need to formalize this what they presented us with what they thought were acceptable approaches. From our point of view, we had these essential elements to work from but they are very general and it took us a while to kind of gear up to say here is exactly what we think--well, not exactly but here is a range of possibilities that are acceptable as an approach, and I think it does vary by the type of study that is actually being considered. That was one of the criteria, for Phase I studies we would do this; for pilots, this. For Phase II and Phase III there were different levels of monitoring that seemed to be appropriate for each of those, both in terms of the type of monitoring and the frequency of kind of review of the data and that type of

thing.

DR. SANTANA: As a follow-up to that, in the non-NCI cancer center umbrella, all the other groups that NCI supports like the consortia, are there also specific requirements for DSMB plans for those consortia?

DR. SMITH: The overall NIH requirements apply to all NIH-sponsored research. Again, those require a data monitoring plan, not a particular form that that plan has to take for implementation. I guess one question here is does FDA want kind of the form and the details, or is it a question of principles, you know, whatever the plan is, it should adhere to these principles?

DR. SANTANA: I think with that comment, I will ask Eric--are you still on the line?

DR. KODISH: I am here.

DR. SANTANA: Eric, can you comment on that in trying to address the issue of global principles, other than specific detail?

DR. KODISH: I would opt for flexibility--

DR. SANTANA: Eric, can you speak just a little bit louder, please?

DR. KODISH: Yes. I would argue for flexibility. I think that the different contexts

of the particular clinical trials involving children with cancer that we are talking about would dictate that it makes more sense to allow a plan based on principles, such as beneficence or such as filtering serious adverse events compared to those that are not as impactful, and I wouldn't try to prescribe the format so much. That would lead to bureaucratization that could actually paradoxically harm the ethical importance of research.

DR. HIRSCHFELD: I would like a clarification from Dr. Kodish. So, would you then say that the principles of, let's say, beneficence and respect contained in the Belmont report and the principles that are annunciated in the ICH documents, for instance particularly the one that applies to pediatric research, E11, are a sufficient statement of the principles?

DR. KODISH: I would.

DR. HIRSCHFELD: I think we can move on.

DR. SANTANA: Before we get to that question though, because I want to make sure that we cover the whole loop of this point, do pharmaceutical sponsors in their DSMB plans have any specific requirements for pediatrics, or are

pediatrics dealt with in monitoring plans as the greater universe of adults? Or has that ever been discussed, that they should develop specific plans for pediatrics?

DR. GRILLO-LOPEZ: Not to my knowledge but, again, I may not be the best person to address that. On the other hand, I would like to comment on the subject of DSMBs because I would not like the FDA to come away from this meeting thinking that there is an endorsement for DSMBs to be required and/or regulated in any way, shape or form. I think that there may be a need for some consensus agreement at the level of professional societies, the NIH and so on, on how different DSMBs might be constructed and when they may or may not be required, but allowing for the flexibility that several around the table have mentioned.

DR. SANTANA: That was my interpretation of the discussion too. I don't think there was any endorsement from this group that we should be moving towards a model DSMB to solve some of the problems.

DR. GRILLO-LOPEZ: I see Dr. Pazdur agreeing with that and I am glad to see that.

DR. SANTANA: I want to clarify that that

was my interpretation too. That is not what I think the comment was all about. Eric, did you want to add anything else? I am sorry, I think I interrupted you. No?

DR. KODISH: No, that is fine.

DR. SANTANA: So, we will move on then from question one--oh, Malcolm, I am sorry.

DR. SMITH: I think those are good principles but I think one can get a bit more detailed without being prescriptive in terms of what the principles of study monitoring should be. For example, the principle that study monitoring should be performed by experienced experts and that that review should be timely, and that whatever the system is, it should have those characteristics. And, study monitoring should be done in a way so that conflict of interest issues are addressed, and that study monitoring in whatever setting, especially in Phase III settings but even in Phase II settings and others is done in such a way that the integrity of the study and the confidentiality of data, when that is important, are addressed. So, I think there are principles of ethics that we need to adhere to and there are principles of monitoring that I think need to be clearly stated

so that you can benchmark how you are addressing those basic principles of monitoring.

DR. GRILLO-LOPEZ: If I may, most of that is already covered in GCP and in other regulations.

DR. SANTANA: So noted. I would only add to that that I think an essential element to that is this concept that I advocate, that there has to be an open communication with the research team, that monitoring doesn't occur in isolation from the actual research team that is conducing the study. I am not implying that the research team should be doing their own monitoring. It shouldn't be interpreted that way but the research team should be integral to that process. Dr. Reynolds?

DR. REYNOLDS: Malcolm, could I just ask you to elaborate on what the role of that DSMB is in the conflict of interest monitoring that you were talking about?

DR. SMITH: What the role of the DSMB is in conflict of interest?

DR. REYNOLDS: Did I hear you correctly? Were you saying that they are really involved in that role?

DR. SMITH: No, that the monitoring is done in such a way that conflict of interest issues

are addressed.

DR. REYNOLDS: In other words, that the DSMB is a separate body and is not subject to conflict of interest. That is what you are saying?

DR. SMITH: Well, that is one way of addressing it but not the only way of addressing conflict of interest issues, but that those issues are considered, both the financial and intellectual conflict of interest that may lead people to ask questions about decisions that are made.

DR. KODISH: This is Eric, in Cleveland. Another way of saying that I think is that transparency is an important principle, perhaps the idea that whatever the monitoring plan is that the appearance of the fox watching the henhouse won't be something that people can interpret as having gone on.

DR. SMITH: The Pediatric Phase I Consortium and the Pediatric Brain Tumor Consortium both have independent data monitoring committees, and these are early phase clinical trials. They are not so much looking over the day to day activities of the consortium and every independent decision, but at intervals they are looking at the overall conduct of how these studies are being done

and are an independent body that tries to address some of the conflict of interest issues, in this case particularly intellectual conflict or kind of ownership conflict issues, and to make sure that the research team is appropriately making decisions as they are conducting the studies. They are there to provide guidance if difficult decisions arise about what their advice would be about how to address these difficult decisions.

DR. SANTANA: If there is no further comment on that we will move on to number two. The next series of questions are more related to reality and practice. Recognizing that particular populations, disease settings, and products may have specific requirements, what general parameters should be monitored for safety in all clinical studies?

DR. HIRSCHFELD: I should say all pediatric oncology clinical studies, just to be clear about that.

DR. SANTANA: So noted. Peter?

DR. ADAMSON: I will take a stab at that. I think it very much depends on the phase of the study. In pediatrics I think we have some advantages in that for Phase III studies there is

probably a general standard of care that we follow whether a child is or is not on study as far as frequency of monitoring. I would say that that would probably be the minimum threshold for Phase III studies.

As one marches down from Phase III to Phase II and Phase I, I think this is where Phase I cancer is different than Phase I "the rest of the world" because we conduct the Phase I studies in patients with the disease. So, I don't think you can layer the same level of monitoring as you do in other studies where volunteers are locked away for two weeks and are plugged into every known device to see what happens. We can't do that.

I think we need to look at preclinical data as far as what potential toxicities are, and in children we have the advantage of looking at the initial adult Phase I experience to see what the relevant additional monitoring might be required. We shouldn't be getting PFTs, echoes, EKGs, stress tests, all the way down the line if, in fact, that is not relevant to a particular drug. So, I think we have the advantage of looking at the Phase I adult experience. Then, we always have to balance the level of monitoring, recognizing that these are

patient volunteers and not normal volunteers as far as trying to strike a balance.

DR. SANTANA: Pamela?

MS. HAYLOCK: I am not sure how relevant this is but you keep talking about monitoring and I think a lot of this has to do with expanding the definition of safety and monitoring in regards to concepts that involve long-term and late survivors. Your institution is maybe somewhat unique in having long-term survivorship programs, but not all places which do pediatric research have such things, and now we are ending up with adult survivors of childhood cancers who are 10, 20, maybe 3 or 4 decades out who are experiencing surprise long-term related effects and I think somehow the parameter of safety and monitoring needs to be expanded. I don't know how to do that but I think the late effects need to be a consideration.

DR. SANTANA: Actually, cooperative groups and other pediatric consortia are addressing that. I mean, I think there is a big effort at the cooperative group level to look at long-term survivor issues in pediatric oncology patients. Obviously, it is in different stages but I think we all recognize as pediatric oncologists that that is

an issue, and I think it is being addressed at different levels. Malcolm and then Donna?

DR. SMITH: It is a critical issue. The challenge with it is that you are looking 10, 20 and 30 years up the road so the infrastructures, like the children's hospitals around the table, need to reach out to a lot of other institutions and to the survivors in order for that work to be done. So, there are different ways that the Children's Oncology Group, the childhood cancer survivor study are trying to address that, and it is recognized as an important issue that we have to address.

DR. SANTANA: Donna?

DR. PRZEPIORKA: I just wanted to ask, the organized groups and the major institutions clearly have a plan but what about industry? I mean, industry does do pediatric trials. What sort of guidance do you give to them, and what is the basis for that guidance? I mean, what has come out of the St. Jude experience monitoring long-term survival in their patients, and is it really worth mandating that the pharmaceutical industry-sponsored trials do long-term follow-up?

DR. SANTANA: I think the issue of

long-term survivorship follow-up and data needs to be considered by the pharmaceutical industry when they are developing a drug in terms of the long-term issues that may be particular to that drug. The problem comes there that the sponsors themselves are limited to a period of time in terms of when they are doing the project with you. Once the project is over, then the responsibility of monitoring patients long term becomes the responsibility of the treating institution. So up front, at least in my experience in all the studies that I have participated in with pharmaceutical industry, I have never really seen, within the context of the protocol, any plan for long-term issues that may arise as a result of follow-up of these patients. Once a study is done, it is done and then it becomes the responsibility of the treating institution to decide what they are going to look for, how it is collected and how it is analyzed. So, there is a little bit of a dis-link there in that we have never really required or asked pharmaceutical industry to address that in the context of the front-line trial that is being developed. Peter?

DR. ADAMSON: Again, pediatrics in this

respect differs from adults because where you really get the long-term ability to look at late effects is in or following Phase III. I am not aware of any industry-sponsored Phase III studies in pediatric oncology. They are almost universally done within the cooperative groups. There are industry-sponsored Phase I and Phase II studies, without question. I think our ability to really ask late effects questions in that population is severely limited so it really becomes the burden of the NCI and the cooperative groups when conducting Phase III trials and, as Malcolm said, there is a whole separate late effects effort. So, I don't think it is something that realistically we can burden industry with because of the likelihood of getting that data in a Phase I or Phase II study. If the environment were to change and we would dream that industry would support a Phase III randomized study in children, then I think we would have to look at the willingness to look for long-term effects.

DR. SANTANA: I will correct myself. I am aware of one study that I have seen, which is an antibiotic study that is actually being sponsored by industry, looking at some issues of long-term

effects of the use of that antibiotic in a pediatric population. It is a very long-term study. It is a very costly study too. So, I am aware of that example that came to mind as I was hearing the discussion but that is kind of unique.

DR. ADAMSON: And it is not anti-neoplastic therapy.

DR. SANTANA: No, it is not. It is an antibiotic study. Any other guidance we can give you on this question, Dr. Hirschfeld or Dr. Pazdur? Yes?

MS. HOFFMAN: I think integral to monitoring safety also in terms of when a child is on treatment is also monitoring participation and entering into the study, and I think we need to monitor informed consents and parents' comprehension of randomization, especially in Phase I studies. Are they really understanding what they are getting into? Also, monitoring waiver of consents because I think there is potential conflict of interest there. The waivers that are coming to the IRB are coming from the PI who is often the clinician as well of the child and, again, there could be conflict there. So, again, I think it is a safety monitoring issue.

DR. SANTANA: I will try and summarize what I heard as committee discussion of this question. I think the committee was pointing out that in a certain way we have a little bit of an advantage in that there may be some adult data before pediatric studies are initiated, and a lot of the safety issues and monitoring that we would want to do in pediatrics have to be put in the context of what data already exist in the adult population that has received those drugs, but also considering that there may be specific niches that pediatrics would provide that we have to look for that may not have been identified in the adults. I heard that comment.

I heard the other comment, that it has to be developmentally phase dependent in terms of what type of study you are talking about, that the issue of safety monitoring is very different in a Phase III trial than it would be in a Phase I, and that there are different mechanisms of reaching those. In a Phase I it may be more the research team, the consortium group continuously looking at that data and making safety judgments, whereas in a Phase III it may be a DSMB or may be other regulatory bodies that can define what safety issues need to be

looked at and how they are evaluated. I heard that comment.

I think the third comment I heard was about this issue of paying some attention to the initial enrollment of patients on studies, pediatric oncology studies, and how we can more effectively not only monitor their involvement but get some degree of understanding of what people really are hearing and their assessment of risk and what they think they are participating in.

Those are the three comments I kind of heard around the table. Susan?

DR. WEINER: I have one more, which is that I really haven't heard any discussion this morning of the notion of safety in trials of biologics where toxicity may not be what you are looking for in a Phase I trial, and it is not clear to me how we might approach that in this context.

DR. SANTANA: That is a good point.

DR. HIRSCHFELD: Noted.

DR. KEEGAN: I think you also should consider that it may be toxicity, it may be other examples but one shouldn't exclude the fact that toxicity could also be a component even in biologic trials.

DR. GRILLO-LOPEZ: I was just going to reinforce what Dr. Keegan said. You know, in the past two years having developed two biologics, they were both associated with some toxicities that were important. So, one has to be careful, going into the development of a biologic, not to think that there might be fewer, lesser toxicities. So, one really has to do the same monitoring that one would do for a chemotherapeutic agent until one is sure of what the toxicity profile is for that particular biologic.

DR. WEINER: Or expand those definitions.

DR. HIRSCHFELD: I think we all agree that the spectrum and the severity may vary but there is no intervention that is risk free.

DR. KEEGAN: Yes, I think the principles Dr. Adamson mentioned were, you know, looking at the nonclinical and adult data to guide what would be used for biologics and even for a lot of traditional drugs, you know, small chemical drugs that are targeted in some way.

DR. SANTANA: Yes, I want to add that there was another point that was made as a general consensus point as advice to the agency that had to do with the issue of neurocognitive development,

and that that may be a particular issue in terms of safety that should be addressed in safety parameters in pediatric oncology trials. In contrast to some of the things that we could capture from adult trials, that is particularly unique to pediatric trials and we should pay some attention to it. Donna?

DR. PRZEPIORKA: Actually, just to follow-up on that, the one other piece of information that I think is very easy to obtain and to analyze is growth.

DR. SANTANA: Any further comments on that question? If not, we will move on to the next question. Based on the response to the previous question, how often should the parameters be monitored?

Here I would say I think we need to be careful. We don't want to get into a prescription plan that everybody has to do kind of in the same way in terms of what things get monitored, at what particular time intervals and how often. I think the idea that I proposed when we looked at our plan at our institution is that it is phase dependent. Once again we go back to the phase issue of the type of study that you are conducting. So,

particular Phase I studies may be monitored more frequently than other Phase I studies. Maybe some biologic studies, gene transfer studies that are Phase I need to be monitored more frequently than an oncology Phase I study.

The point I want to make is that although it is phase dependent, I think also in the formula has to be included the specific agent that you are testing in that phase in order to decide how often you are going to monitor it. Peter?

DR. ADAMSON: Yes, I would echo that. Again, going back to the adult experience, it gives us an advantage as far as what to expect and when to expect it. But the other thing that we sometimes err on is that we have to look at our own definitions of toxicity and what we consider either serious or dose-limiting because when you look at those definitions, you then look at how frequently you are monitoring and you realize you will never be able to meet those definitions. So, as I said, perhaps a simple starting place if you want to get some idea of what the spectrum is, there a number of cooperative groups or a number of single institutions that conduct this and my guess is you will find a common thread in the backbone of those

that apply across the board for Phase I and a different set for Phase II and then it becomes very agent dependent beyond that.

DR. PAZDUR: I have a question as far as the toxicity criteria for children, are there any differences between that and what we use for adults, other than perhaps physiological differences that may exist with growth parameters? What I am after is some of our adult toxicity criteria have some subjective elements as far as elements of daily activity, fatigue, etc., and how do you figure that into toxicity assessments with children? Or, do they have difficulty in assessing some of these toxicities in children? You know, for some of our activities for adults neurotoxicity might be difficulty in buttoning your shirt or in adult activities of daily living in a sense.

DR. SANTANA: Alice, it looks like you wanted to respond to that.

MS. ETTINGER: Well, I think we all understand that for kids we have to look at them at an age appropriate level and many times that would be school attendance, how they are functioning in school, certainly measurements of that sort. I think in terms of fatigue, we are way behind in

measuring the actual fatigue level that we may be seeing in children, not only little ones but certainly as they grow up. Often in filling out the forms for doing the criteria, I feel that there may actually need to be other criteria that we look at and that we measure for children.

DR. SANTANA: It is a good point. The issue with those criteria is that as yet they haven't been validated so it is very hard to apply them across studies but there is actually a lot of research going on in that field that, hopefully, in the next few years will give us some guidance. But that is the problem, those criteria are soft and they haven't been validated so it is very hard to apply them. So, in oncology we kind of rely on the standard toxicity criteria that was developed by NCI, etc., in terms of what we look for and how we code it.

DR. HIRSCHFELD: I will just add to that. There have been questions raised about having some pediatric specific scales, but it was the absence, as Dr. Santana pointed out, of having validated assessments that has precluded from formally incorporating those. So, that is an area that still remains under discussion and has had some

interest for some years.

DR. ANDERSON: And in the current version of the CTC, the updated version that just came out, where possible, all distinctions between pediatric and adult criteria were eliminated because basically we generalize the grading. I can't remember exactly what word you used, Dr. Pazdur, in terms of the degree of toxicity. You know, just having treated patients with different pediatric cancers and actually having heard from people who are trying to set up studies with certain dose-limiting toxicities, in pediatrics a lot of times I think the dose-limiting toxicities that we accept are greater than are accepted in adults. They will stop an adult trial or they will change an individual adult's treatment much sooner than we do in pediatric oncology and I don't know that we have different measurements of toxicity but we would move a grade further perhaps, or half a grade further in terms of maybe the duration of the tolerance of a toxicity than happens in medical oncology.

DR. SANTANA: And those are usually specifically defined within the context of a protocol. So, for some studies we would accept up

to grade X and in others we wouldn't. So, I think there is a lot of variability and it is really driven by the protocol and the question you are trying to answer and what you know about that drug beforehand.

The next question is based on the response to the previous question, who should do the monitoring? Is it adequate to have the personnel involved in the study be responsible for safety monitoring? Susan?

DR. WEINER: The issue of the conflict of role between the investigator and the treating physician is something that has been discussed over the past few years in a variety of contexts. I think that applying that notion to this, it becomes obvious that such a team is insufficient.

DR. SANTANA: Peter?

DR. ADAMSON: I guess I would disagree with that to an extent. It very much depends I think on the phase of the study, and the number of children who are at risk, and what the goals of the study are. From a practical standpoint, for a Phase I where the study is a real-time study that is the role of the study team. They are making a decision on a patient to patient basis. Having an

additional layer of oversight to make sure the study team is meeting its obligations I think is helpful and is important but, from a practical standpoint, you can't convene a data safety monitoring board with every dose escalation step; you never would end up conducting the study.

Having said that, it is important to keep in mind that the goal of a Phase I study is to recommend a dose and so the study is going to be successful really no matter where you stop as far as an investigator conflict of interest. I mean, they will meet their study endpoint. Having said that, when you come to a Phase III, you really do need additional layers of monitoring because then you really want to prove is this drug effective and there is a lot riding on the outcome of that study.

So, the level of monitoring I think very much depends on what the phase of the study is. But I think, without question, you need to know what the data safety monitoring plan is. I mean, investigators need to be very clear and very specific up front about how this study is going to be monitored. I will come back to what Eric Kodish had said earlier, you need to have some flexibility as far as what the level of monitoring is and who

does it. If it is a cytotoxic and there is a lot of experience in developing the cytotoxic, that may lead to one level. If it is an entirely new modality of treatment being put forward, you may want to consider another layer of monitoring. So, there has to be some flexibility within the system.

DR. SANTANA: I would echo what Peter said. I think it is a graded system and it depends on the type of study you are doing and what elements are being monitored. For example, if you want to get into the nitty-gritty details of monitoring enrollment and informed consent, I think that has to be independent of the research team. There is no other way you could do that; it has to be a separate monitoring group that does that, whether it is the protocol office or another group of people. But in a Phase I study if the central question is the toxicity, that should be monitored by the study team because that is what is going to define how the study progresses. Then you may have intervals in which that data is shared with a central Phase I group, etc., etc.

Whereas, in a Phase III study you are in a completely opposite direction. For a Phase III study most of the elements for safety that you want

to monitor have to be done independent of the investigator. They are large group studies with data collection. There may be some safety issues that have to be reported to the safety data monitoring boards so you have to use those resources.

So, I don't see it as black and white. I see it as a graded system in which the elements that are going to be monitored, the safety and how that is done may incorporate different groups and you just have to find the right fit for the study that you are considering. I hate to put it in black and white; it won't work if it is black and white. I think the beauty of some of the stuff that Peter mentioned in terms of what the Phase I and the COG Consortium is doing is that they are doing it in real time. I mean, they are looking at that week by week, maybe two weeks or however often, so they have the advantage of doing that in real time so that they can intervene if they have to. Whereas, I think that would be impossible to do in a Phase III study. You just couldn't get people to do that. Dr. Reynolds?

DR. REYNOLDS: Peter, acknowledging the challenges you put forth that a data safety

monitoring board in a Phase I study--that it is not practical for them to convene and review, I think we should acknowledge that there are some significant advantages to having such a board for the day to day people that are monitoring to go to with questions about study design amendments that might make it more acceptable from a safety standpoint, and having that group that is external to the people who are actually conducting the study. It is a small world in pediatrics, so having that separated out, at least from the NANT perspective, is a great advantage in being able to bounce things off these people externally.

DR. SANTANA: Dr. Smith?

DR. SMITH: We talked about NANT trials, COG trials and we are very restricted to that. Would there be a separate answer for industry-sponsored Phase I/Phase II trials? Is that a different situation?

DR. SANTANA: Usually in Phase I industry-sponsored trials, at least the ones I am familiar with, there is a research team that is identified. It is usually the PI at various institutions; it is a medical officer or monitor from the pharmaceutical company or contact person.

I think the same functional principle can be applied, that that research team should communicate frequently and often enough as the study is being conducted to make ongoing decisions about the safety of the study. So, I think that may already be happening. We just don't know about it. If it is not happening, we should probably extend those things that we are doing in some of these consortia to those. I think they are practical and they don't require a lot more work.

DR. GRILLO-LOPEZ: If I may expand on what you said, which is absolutely correct, there is a research team in a pharmaceutical industry-sponsored study. Beyond that team, within the company itself, there is also the equivalent of a data monitoring board which usually consists of the project clinician, the safety officer and the statistician as a minimum. The data is looked at very frequently. In addition to that, there are periodic presentations of the safety data to larger committees within the company and then there is an opportunity to also present that data, if there are any red flags, to the scientific advisory board of external advisors which usually meets three to four times a year depending on the situation.

DR. SANTANA: Donna?

DR. PRZEPIORKA: Actually, it sounds like industry has a separate oversight; the organized groups have a separate oversight; NCI-sponsored studies will have a separate oversight. What we haven't discussed is individual investigator-initiated studies at single institutions. I think under those circumstances it might not be too disruptive to say, you know, at some point see if there is somebody who can give you an outside reality check before you go on to the next level. It may not require convening an entire board but just sending a member to the IRB or to whatever institutional data safety monitoring committee might be available.

But, you know, having conducted Phase I studies, one can get lulled into, okay, I have five more patients lined up; let's go to the next level before I really have all the data collected on safety. It may be just enough to actually improve patient safety at that one institution.

DR. SANTANA: Yes, I am glad you mentioned that. We tried to address that at St. Jude. As an academic institution, we tried to address that too with some of our own Phase I studies. So, we

operated very similarly to what the Phase I Consortium is doing, and that is that if it is an institutional Phase I study the research team meets frequently to review, as the study is being conducted, what the safety concerns are; what is going on with the next escalation, etc., etc.

Then there are two separate groups that also look at that. There is a separate Phase I/II planning group that we have that includes disciplines from solid tumors, leukemia, transplantation and biostatistics, all the basic science people and they are also supposed to meet every month but in reality they probably meet every six weeks and all the studies are also actually presented very briefly. So, the whole group knows where each study is going and what is happening with toxicity; what is happening with issues of accrual. That is not truly separate because it is constituted by individuals from the same institution.

The third layer is that even for Phase I studies-- if you saw in my flow diagram where data went, all the adverse events, independent of any type of study, also get reviewed by the clinical protocol scientific review group subcommittee which

does not include any of the Phase I PIs. They also make a judgment in terms of how that study is going; in terms of dose escalations; in terms of safety. So, it is very similar and kind of a little bit of recapitulation of what the cooperative group is doing in terms of having other people look at it. It is not totally independent in the sense that there is an outside group that looks at it.

Having said that, also in some Phase I studies, like the gene transfer studies--when we get to the question of DSMB committees I was going to mention that, we have a definition of what gets referred to DSMB and one of the definitions is if there is a Phase I study that includes gene transfer or a biologic that is potentially problematic, that will go to the DSMB although it is a Phase I study. Barry and then Susan?

DR. ANDERSON: Also, being part of this review board at the cancer center data safety monitoring plan, anybody who is receiving a grant that might involve a clinical study as an individual also has to provide a data monitoring plan in order to receive the money for the grant.

DR. SANTANA: Susan?

DR. WEINER: Just a point of clarification, just to make sure that the following case is covered for Phase I and perhaps for Phase II in pediatrics, let's say a network of institutions that are doing combination therapy trials, pharmaceutical trials, and they are not being supported by NIH--presumably the institutions have assurances, etc., but the monitoring of that particular kind of trial.

DR. SANTANA: Do you want to address that because it is primarily coming from the issue of industry-sponsored small trials within two or three institutions? Am I correct, Susan?

DR. WEINER: Or more.

DR. SANTANA: Or more. Do you want to address that?

DR. GRILLO-LOPEZ: From the safety point of view, they are monitored in exactly the same way that I mentioned earlier.

DR. WEINER: Well, just in terms of the external terms. So, the company sets up some external monitoring to review safety concerns--I mean, if it is two drugs--

DR. GRILLO-LOPEZ: Well, if it is a Phase I or Phase II trial usually there is no external

review, external to the company review, other than that the company has to report to the FDA. So, that is an external third party. Also, the company has the possibility of presenting the safety information to the scientific advisory board which is also an external review board.

If there is a Phase III randomized study, particularly a blinded study, most companies are opting to have an external independent data safety monitoring board following that study, or if it is a Phase II trial that is already randomized and blinded.

DR. SANTANA: Any other comments or questions? Then we will move on to the next question which is asking us for advice on what circumstances would benefit from a data monitoring committee/data safety review board oversight?

To try to address that, I think Barry had in one of his slides what some of the recommendations are from NCI regarding--or was it COG? I don't remember that.

DR. ANDERSON: Recommendations from NIH.

DR. SANTANA: Do you want to expand on those, Barry?

DR. ANDERSON: In pediatrics the default

seems to have some sort of monitoring committee, a more formalized monitoring committee because the recommendations were if they were complex--and if you have ever looked at an ALL study or anything else, they are pretty complex, and every study basically, if it is multi-institutional, which pediatrics for the most part usually are--if it is a vulnerable patient population, and we have our own separate part of the regulations just because pediatrics is a vulnerable patient population, and high-risk treatments--you know, a lot of the treatments that we use with stem cell transplants, etc., etc., are high risk. So, because of all those issues coming up in a lot of cases, a data monitoring committee is involved. It may be different than a DSMB that you were talking about for a Phase III randomized study because some of these monitoring committees also work for single-arm studies that may have early stopping rules that need to be interpreted, and that sort of thing as well.

DR. SANTANA: I would add two additional items to the list that Barry proposed. As an institution, there are two other types of studies that we would refer for an independent data safety

monitoring board. One is any study that involves any type of gene transfer or biologic that potentially could present a hazard to children in the future. Then, the second is a very unique type of study which is what we call the window study where an experimental therapy is given prior to conventional therapy and there is a limitation of time in which you can really do that to provide safety for the patients. So, those kind of studies we would also refer to DSMB to provide oversight.

Any other comments or questions on that? Yes?

DR. GRILLO-LOPEZ: A clarification, when you made your presentation you mentioned the makeup of your data monitoring board and you said it was the staff involved in the study itself, the principal investigator and perhaps some others around the principal investigator, and then some additional members outside of that group. But should I interpret "outside" as within the cooperative group or completely external to the cooperative group?

DR. ANDERSON: It depends on whether you are talking about a DSMB or a DMC. I mean, there has been some distinction there. The DSMBs would

be probably reflective of what industry uses when they have an outside independent one. For the COG DSMBs there is a member or maybe two members of COG that are part of that but there are statisticians from other adult cooperative groups. There are outside lay people that are part of it, and there is a government representative there. It is set up such that the vote could never be carried by COG members. And someone who would be perhaps a study investigator for a particular Phase III study, they would not be involved in discussions of their study if they happened to be also a COG representative to the group.

For other data monitoring committees--I can't speak for Peter's group but for the NANT that data monitoring committee has one representative from that group or institutions that are conducting these early phase studies. A number of people are COG members but they don't participate in these studies. There are other people who are retired pediatric oncologists. We have statisticians from outside the group. We have lay people from outside the group. So, again, we are not looking at Phase IIIs, we are looking at early studies. Again, the predominant role is that you are outside of the

people who are doing the investigations. That, again, is for the interval of about every six months of formal review but also being there as a resource ongoing.

The reviews that go on in the NANT group sort of on a more frequent basis could involve study investigators but it is usually the bigger group of other investigators that are part of the group but not responsible for that particular study. So, there is some oversight in the sense that it is within the group but it is not the person who has the most vested interest that that single study succeed in one way or another.

DR. GRILLO-LOPEZ: It is probably worthwhile to mention that in industry today most Phase I and II studies have an enrollment period that ranges from 6 months to 12 months and perhaps not more than that. So, the value of an external data safety monitoring board is limited because of your ability to actually give them trend information and so on when you have actually completed enrollment on the study.

DR. PAZDUR: I would just like to mention that we have a draft guidance on data safety monitoring.

DR. SANTANA: I think with that we will go to the last question, which is an open-ended question, are there additional recommendations for safety monitoring? Peter?

DR. ADAMSON: I think the only one that came up earlier is that institutions don't have adequate resources to do this job well. That is not unique to pediatrics but every layer of monitoring that gets put on an institution and investigator--you have to look if the resources are there to truly meet it. I think in most institutions the resources are inadequate right now.

DR. SANTANA: I would echo that. I think we started this morning's session with a comment about stewardship and I think stewardship includes financial resources so I think the regulatory agencies need to be very cognizant that if we are going to do this, there has to be a mechanism to provide monies to do this well. There can't be mandates without monies to actually carry this out well. Susan?

DR. WEINER: I have one additional comment, and that is that I think that the term "lay member" is fine but it seems to me that when

one is reviewing pediatric trials there really ought to be a family member who is that lay person to help assess the safety of the situation.

DR. SANTANA: Good point. Any other comments? Any other guidance that the FDA wishes from us on this session? If not, we are adjourned for the morning. Thank you. We will try to reconvene at about 1:15.

[Whereupon, at 12:25 p.m., the proceedings were recessed for lunch, to reconvene at 1:20 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. SANTANA: Let's go ahead and get started with the afternoon session in which we are going to talk about preclinical models and other data that we could extrapolate in terms of helping us design clinical studies. Before we get started with the actual presentations, we need to go around the table again and re-introduce ourselves because there are new individuals who have joined the group and, hopefully, not many others have left. So, can we start with Dr. Anderson, please?

DR. ANDERSON: Barry Anderson, from NCI CTEP.

DR. HOUGHTON: Peter Houghton, from St. Jude Research Hospital.

DR. ADAMSON: Peter Adamson, The Children's Hospital of Philadelphia.

DR. HELMAN: Lee Helman, Pediatric Oncology Branch, National Cancer Institute.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, NCI.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, Neoplastic and Autoimmune Diseases Research Institute.

MS. HAYLOCK: Pam Haylock, oncology nurse

and ODAC consumer representative.

DR. PRZEPIORKA: Donna Przepiorka, University of Tennessee, Memphis.

MS. CLIFFORD: Johanna Clifford, executive secretary for this meeting. I am just curious, is Eric Kodish still on the line? No.

DR. SANTANA: Victor Santana, pediatric oncologist at St. Jude's Children's Research Hospital, in Memphis, Tennessee.

DR. REYNOLDS: Patrick Reynolds, Children's Hospital of Los Angeles.

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

DR. WILLIAMS: Grant Williams, Oncology Drugs.

DR. KEEGAN: Pat Keegan, Oncology Biologics.

DR. HIRSCHFELD: Steven Hirschfeld, FDA.

DR. DINNDORF: Pat Dinndorf, Oncology Biologics.

DR. DAGHER: Ramzi Dagher, Division of Oncology Drug Products, FDA.

DR. SANTANA: Thank you. With that, we will go ahead and get started with the first

presentation, Dr. Paul Meltzer.

What are Microarrays and How Can They Help Us with Clinical Studies in Pediatric Oncology

DR. MELTZER: What I am going to do is to very quickly give the members of the committee a tour of some of the clinically relevant applications of genomic technologies involving microarrays which may have a bearing on some of the issues that you are considering today. I will do that in the fashion of a very brief overview of technology in a few specific examples, and give you my impression of some of the issues that would have to be overcome for this information to be evaluable in clinical trials.

Array technologies have now been around for several years, and the ones that I am going to talk about mainly today are actually becoming rather mature, and it is now possible to generate data with these technologies which can be considered sort of archival quality that will serve as a long-term source of information about the diseases that are being looked at.

There is some the excitement around these technologies, as indicated by this slide which just shows the number of citations in PubMed on

microarrays from the inception of the modern technology for microarray expression profiling through last years. There has been an exponential growth in the number of publications that cut across all areas of biomedical research. There has been a tremendous amount of interest and activity in data generation, importantly, for you to consider.

The reason that this momentum has built up has been based on the availability of the human genome sequence which now allows a whole genome approach to identifying the genes expressed in tumor tissue samples or in the context of other types of biological samples. Of course, this will include drug targets and, indeed, it should include every conceivable protein drug target, as well as gene expression signatures which represent a cellular readout that is associated with important clinical or biological properties of cancers. I will try to explain this concept with just a few examples in a moment.

There are a number of different microarray technologies and I am just going to be touching on the two that are underlined because these are the ones that are in most widespread use today really

throughout the world. At the top of the list, and mainly what I will be talking about, is expression profiling, measuring the expression of large numbers of genes in parallel in a given biological sample.

It is important to note that there are other array technologies coming along which are likely to have a role of some type in clinical application, and that includes microarrays to determine DNA copy number in tumors, or CGH arrays, microarrays which can determine DNA polymorphisms, commonly referred to as SNP chips. I am going to touch briefly on tissue microarrays because they have emerged as a very important confirmatory mechanism for the RNA-based expression arrays which are also potentially of clinical importance. Of course, protein arrays, various forms of proteomics, are important and I am not going to talk about that.

It is important for you to realize that there is a tremendous amount of gene expression data, mainly from adults, which has already been generated with these technologies, and a great deal of this is already publicly available in databases that are universally accessible.

So, this is just what one form of microarray looks like, basically a glass microscope slide on which DNA probes have been deposited. I won't dwell on the technology, other than to point out the important feature, and there are several different embodiments of the technology but the important feature is that we now can look at the entire human genome, or animal genome if you are talking about an animal model, cramming in the entire genome on a single microarray chip and it is possible to interrogate this chip, to use it to interrogate a biological sample to look at expression of all the different genes in the human genome in a biological specimen. For those of you who are into gene expression, you know that there are subtleties involving, let's say, splice isoforms and, indeed, that is being looked at with this type of technology as well. So, you can really get a very detailed picture of expression across the genome at the RNA level with this technology, and one that is actually remarkably accurate and carries with it quite a nice snapshot of an individual biological sample.

So, what are some of the potential connections between this information and cancer

therapeutics? The first I would mention is to increase the precision in tumor diagnosis to complement additional pathologic techniques, and perhaps to identify and define subsets that haven't been previously recognized in previously thought to be homogeneous tumor groups; to measure the expression of drug targets; to recognize signatures, and I will expand on this in a minute, which might be associated with the activity of a particular drug target; to identify features in the gene expression profile which might be related to drug sensitivity or resistance; and potentially to monitor or predict toxicity.

Now, there are subtleties and, in fact, it is actually an extremely complex topic, the analysis of microarray data that I am not really going to touch on, but it is important for me to point out to you that aside from simply scoring in a simple kind of plus/minus way for the presence of a given gene or target, all of these types of analyses require a training set of tumors to identify the relevant genes and to develop a scoring algorithm which can be used to look at these various types of readouts.

Another very important feature of this

data is that if you have full genome data it is comprehensive. It is intrinsically comprehensive. There are only so many genes in the human genome; there won't be more in five years than there are now, or in 10 years or in 20 years. That is why the data has a very nice archival quality to it. So, it can be reanalyzed in the future with respect to novel targets or signatures that might be identified so you basically have data that really won't go stale so long as it is collected in a state-of-the-art fashion and is appropriately archived.

This slide just outlines the strategy that is used in microarray studies. You start with the whole genome and look at a very large number of genes, so tens of thousands of genes across many samples to develop profiles that occur in a particular clinical situation. Then you go through some process of gene selection to identify those genes which separate tumors or patients into groups according to the particular question that is being asked, whether it be drug response, toxicity or a diagnostic question, genes that are associated with a particular target activity, and so on.

You then have to go through a process of

validation, frequently involving a new sample set and reiterating this process to validate it, and also probably validating it with other technologies such as RT PCR, quantitative PCR or immunohistochemistry or RNA in situ hybridization or something like that to validate the results. You might want to proceed to a clinical assay development, and it is very important to point out that much of the momentum in the development of clinical assays based on this type of information involves not microarrays but other forms of multiplex gene analysis which might involve, for example, a PCR-based method.

So, this is the overall approach and here are going to be a couple of very quick examples. This is from a study we published several years ago identifying groups of genes that separate for common pediatric cancers, Ewing's sarcoma and neuroblastoma, rhabdomyosarcoma and Burkitt's sarcoma. Color-coded here and at the top of this clustergram, each of these little groups of red squares represents groups of genes that separate these groups of tumors and can be used to diagnose them with a high degree of accuracy.

The important point about this slide is

that out of a large number of thousands of genes, the genes that were necessary to give a perfectly accurate call involved a very small number of genes, about a 100 genes, 96 to be precise, which were identified by a process of gene minimization. So, that is the bottom line of everything that you will see in the literature or hear about, that one doesn't need tens of thousands of genes to answer a question. If it is possible to answer it, usually a very small number of genes, less than 100, will be sufficient to accomplish what you want and sometimes as few as two.

I am going to give two quick examples that illustrate these features in detecting therapeutic targets by microarrays, one in gastrointestinal stromal tumor, or GIST, and the other is breast cancer which involved a couple of studies that were from our lab.

In the case of GIST, here were are seeing the separation of gastrointestinal stromal tumor from non-GIST sarcomas with, again, the minimal number of genes necessary to establish the separation. The important point for today's discussion is that when we looked at the top genes we found that the KiT oncogene was actually the

number one gene. So, we both could score the presence and assess its relative importance in characterizing this particular tumor in one process, and one can do this in respect to any property of a tumor that you choose. So, this is an example of scoring a single gene out of microarray data.

If you will forgive me for introducing an adult example, I will now give you an example that indicates how you might work--

Oh, this is just to show how KiT looks on a heat map of GIST versus non-GIST. You see this very uniform pattern of KiT expression.

I will give an example now of how you would look at a signature for gene expression using the estrogen receptor in breast cancer which, of course, is a very nice molecular target widely used in breast cancer therapy. The point here is that there is a distinct pattern of gene expression in breast cancer that separates the positive from negative tumors very sharply, and everybody who looks at these tumors has found exactly the same result. It is the strongest feature in gene expression profile of breast cancer.

Importantly, it is possible to actually

predict the value of the protein measurement for ER in a tumor specimen from the gene expression profile using a number of genes to make that prediction excluding the estrogen receptor itself. So, you can actually plot on this figure the actual ER level in the little magenta circles, and the predicted value based on the gene expression profile based on a group of several hundred genes in these tumors. So, there is a signature that goes with the presence and function of this particular drug target that can be read out using multiple genes. Similar observations have been made for other targets. So, this is an example of a multiple gene predictor.

The bottom line here is that microarrays can measure therapeutically relevant genes either as individual genes or as complex signatures, and expression profiling then can reveal both the presence of a target and measure relative abundance within the cell at the RNA level. Finally, a signature related to target function can reveal its level of biological activity, as in the ER example.

I just want to take a couple of moments to talk about tissue microarrays because I think these are very important and very accessible from a

technological point of view. A tissue mircoarray is simply an array taken from paraffin blocks from patient samples, assembled into an array which can then be sliced to produce many slides that can be assayed for various markers. The power of this technology is that, in contrast to the DNA microarray in which we measure thousands of genes, for each tissue specimen in the tissue microarray we can measure one gene in thousands of specimens very rapidly. So, these are very powerful tools for the validation of findings for genomic surveys and potentially for translating them into clinical studies.

Just to emphasize the tremendous advantage that we gain from using these arrays, it arises from taking a large number of paraffin blocks and condensing them down into one very affordable, economical package where we can survey single tumors with a slice from any individual tissue microarray. So, it is a very powerful technology that I think can be quite useful.

So, how might these technologies be implemented in clinical trial designs? I just want to take a moment to give you some perspective. First of all, to reiterate, detection of individual

targets is really simple. That is not difficult and is very straightforward and should pose no real challenge. However, in terms of using this for pediatric cancers, we have a problem in that so far only limited data is available on pediatric cancers in the public repositories and that would be one of the major obstacles. Indeed, very minimal data exists relative to any question of toxicity, and these are issues that are just beginning to be seriously looked at in adults and, to my knowledge, haven't been examined in children at all. As far as I can see, implementing tissue collection protocols and microarray analysis as part of ongoing trials would be a necessity to overcome this limitation.

Tumor tissue sampling is essential to get a picture of the tumor but I am not sure that it is necessary to have serial sampling. It would be in principle nice to know what happens in the residual tumors of patients who don't respond to therapy but in principle this should be predictable from the initial signature.

It is also interesting to speculate that useful information regarding toxicity may potentially be obtained from blood samples for

example, but the data to support this concept is extremely limited at the present time.

Finally, again to reiterate, complex questions such as the prediction of response or toxicity require a training set and can't be answered a priori or predicted from a bunch of array data. So, if we want to talk about taking array data from an archive and predicting what might happen in those patients in response to a particular agent, we really don't have a way to do that at the present time. The only way we can really examine that is to have samples annotated with respect to that clinical question. So, that is basically what I had to say. Thank you.

DR. SANTANA: Thank you. We will have some opportunity during the discussion period to address some questions. I think Dr. Peter Adamson is next. Peter?

Advantages and Limitations of Cell Culture Models in Pediatric Drug Developments

DR. ADAMSON: For those of you who remember Monty Python and now for something completely different, whereas microarrays are approaching their tenth birthday, cell culture models are probably approaching retirement age.

So, what I thought I would do is speak briefly about some of the advantages and limitations of these models. Historically, they have been controversial as well as helpful. I think many of the issues that occurred historically are still issues today.

To really understand that, I want to take you through a very brief history of cell culture models in the context of drug development. In looking back, probably the clonogenic assay is a good starting point as far as how these models have been used. This was work done by Hamburger and Salmon, published back in 1977 in Science. What they were able to show was that they could take a number of primary human tumors and grow them up in a cell culture matrix.

This is a photo micrograph from their publication. Definition tumors have different colony formations but the concept was that these represented tumor stem cells, and stem cells were the renewal source and they served as a seat of metastatic spread, and cytotoxicity in this assay was going to be proportional to cytotoxicity in vivo. If you didn't get at the stem cell, you weren't going to have an effective anti-cancer

treatment.

The way the clonogenic assay worked when it came to cytotoxicity is you would expose your culture media to various concentrations of drugs and then look at the effect on colony formation, look at the clonogenic assay.

Predating the clonogenic assay there were other mechanisms to try to look at cell growth and behavior in vitro. The tritiated thymidine assay was probably the most common one. This was a pretty straightforward approach where you would tritiate thymidine and measure the incorporation into dividing cells. It basically was a measurement of S-phase cells and it quantified that simply by counts per minute with a radioactive label.

There were clearly limitations really to both of these approaches. The clonogenic assay was very labor intensive and there were a number of investigators who, despite that hurdle, ran an incredible number of assays looking for activity of cytotoxic agents. But the reality was that it was really not readily amenable to high throughput.

Conversely, the tritiated thymidine, although there were the limitations of just using

the radioactive label, was also a non-clonogenic method. You are looking really at a different endpoint.

Then the field began to change and began to change based on a paper by Mossman, an immunologist, in The Journal of Immunologic Methodology, in 1983 when he described what is an assay familiar to almost everyone, the MTT assay which was a colorimetric assay for cellular growth and survival. In this assay a salt, MTT, when incubated with viable cells in the mitochondria undergoes a ring opening and produces a purple salt, formazan. Then you solubilize this; you get a purple color and you put this in a plate reader and the intensity of the optical density is proportional to the cell number. This assay really began to change a lot of what was happening in the world of cell culture and cytotoxicity.

Perhaps in part where it had a great impact was at the NCI which, at this time, was looking at moving from their historic way to screen compounds for anti-cancer activity to what became known as the NCI 60 cell line screen. This is a typical output on a plot of logarithmic concentrations of a drug as well as survival. As

many people have noted in the past, the 60 cell line incorporated a number of malignancies--leukemia, non-small cell, small cell and so forth, but there was ne'er a pediatric malignancy on this list. There were many efforts made to try and change that and probably, in hindsight, it was probably just as well that we didn't.

Nonetheless, in the late '80s, early '90s and even today there are a large number of clonogenic assays that were based on the MTT, XTT. The SRB assay, sulforhodamine blue, was the one that the NCI eventually adopted; historically trypan blue uptake in viable versus non-viable cells; and the list goes on and on. Each of these has various advantages and various disadvantages but ultimately they are all measuring a very similar endpoint and these are non-clonogenic assays.

At this point it is helpful to step back and say, well, what are non-clonogenic assays, when it comes to drug development, really telling us? What principles do they rest on? Taking some liberties, I think these are the assumptions that are made. As you can see, many of these

assumptions are supported by data, others less so as we work down the list. But the non-clonogenic assay is really a measurement of viable cell number and almost all the non-clonogenic assays do that to a reasonably good degree.

Many of these have been correlated which is considered in vitro the gold standard, the clonogenic assay. Again, not all of them, and it is very cell line dependent how well that correlates. But then one starts making larger leaps. That is, that the clonogenic assay somehow is correlated to in vivo cell growth and in vivo cell growth that is somehow correlated to the tumor growth in the patient. So, when you start up here you have a long list to go down as far as what we are asking an assay to do as far as being able to predict or not predict what is going to happen in a patient.

Let me talk about some of the potential uses. I mentioned drug discovery and this is an output from a more recent NCI screen. This has advanced as far as the type of information that comes back. There is a compare algorithm that can talk about mechanism of action, and so forth, but if you put it in the broader context of drug

discovery, this is not how drugs are discovered today. I mean, in industry today you have a target; you develop an assay for a target and you, hopefully, have an assay that is amenable to high throughput. For the most part, outside of the 60 cell line screen, this is not how drugs are being discovered.

But cell culture models are still useful in a number of areas. You can study cellular pharmacology. You can certainly study mechanism of action of drugs in these models, as well as evaluate drug resistance.

Now, as pediatric tumor models, they have historically and continue to serve at some level as a screening for drug activity, but you can also ask dose or, more appropriately, concentration schedule dependent questions in cell culture models and one can evaluate drug combinations in these models.

There are, not surprisingly, limitations. Some of these limitations are unique to in vitro models; some can be transferred over to in vivo models. We know that cell lines undergo transformation to allow for in vitro growth. For in vitro drugs that require metabolic activation or have active metabolites, you are likely to miss

that. You are not likely to be able to pick that up given the nature of the in vitro model.

There are clearly potential differences in drug exposures in these in vitro models. They can range from differences in protein binding. Drug disposition is incredibly difficult to try to model in vitro. You basically dump the drug in and you let it sit there for a period of time. That is not what happens in a patient as far as how drug is cleared. There are certainly differences in tumor micro-environment or lack of vascularization and hypoxia. There are methods, and Pat has looked at some methods, to try to compensate for that in in vitro models to try to better reflect what is happening in vivo, and there are many other limitations.

With that background, there are still some advantages to these models. Relatively speaking, these are not labor intensive models. They are relatively low cost and they are amenable to moderate throughput. In addition, because of these, you have the ability to study multiple cell lines and I think, perhaps as we move forward in product oncology, the ability to study multiple combinations of drugs.

One advantage of the in vitro model I think over other models is that it is probably the only model system that is mathematically amenable to defining synergy, additivity or antagonism. It becomes very complex in other systems to really know if something is synergistic or not. There are a number of accepted methods to do that in an in vitro system.

So, let me start there and I am just going to share three very basic examples of in vitro models and what they can do, and I think I will be commended then for picking up the pace as far as getting us back on whatever time line we should have been on.

The first one is determination of synergy. I know folks in the room know this, there is a problem with a simple addition method. If your drug A kills 15 percent and drug B kills 25 percent, well then, if the combination kills more than 50 percent it is synergistic. Well, it doesn't take much to realize that you run into a problem pretty quickly if drug A kills 70 percent and drug B kills 70 percent. You can't simply add them up. We can't just say, aha, it is synergistic; it is more than the sum. That is what

we are sometimes left with, with in vivo models but it is very difficult to know that. There are a number of mathematical approaches and these get debated constantly in journals that I don't like to read--

[Laughter]

--but they do get debated. One of the more accepted models is the median effect model. There is now software that really can make this very user friendly and straightforward. But if you have different drugs you first look for a rational effect as a concentration of dose and you do that with one drug; you lay on the other and you lay on the third, and then you realize you can't see what is going on. So, you transform the data and you get what is called a median effect plot. From the median effect you can calculate what is called a combination index. Please don't try to figure this out from the graph, but let me tell you that the software will basically tell you, yes, it is synergistic or it is additive, or no, in fact, it is antagonistic. There are other methods and probably all of them are reasonable methods to look for whether a combination is going to be synergistic.

Other examples, and this is probably where this has been most widely used, that is, is this drug that is being developed in adult malignancies relevant to pediatric malignancies? Does it have activity in pediatric tumors?

So, I chose a relatively recent example that Beth Fox is working on at the NCI, epothilone B, a Bristol-Myers drug. This is an analog that binds tubulin. It stabilizes microtubules by inhibiting tubulin depolymerization, blocks mitosis and causes apoptosis. Interestingly, this drug is cytotoxic in Taxane resistant tumors, as well as in cell lines that over-express MDR. So there was an interest certainly in the pediatric community as far as is this a drug that we should be looking at.

So, what one can do is one can look in vitro. In general, it is always helpful to have some sort of reference base to compare your drug with. In this case, we compared it to other microtubule toxins, paclitaxel, vincristine and vinorelbine and looked at the concentrations that were required to produce cytotoxicity in an in vitro model. You can look at these and you can say, well, for these drugs, in fact, these are concentrations that fall within the range achieved

in patients, and then you look at the drug in question and say, well, these are the concentrations that, if this model is predictive, one might anticipate needing as far as a relative effect and one can ask if there is adult Phase I data or are these relevant concentrations.

In addition, one can do some pharmacodynamic work. In this case, one can look at the concentrations that were effective. Were you hitting your target in a very endpoint type of way before cytotoxicity? What was the effect on the polymerization versus non-polymerization? That is what Beth did in this study. So, it is helpful as far as an inexpensive way to look across a panel of cell lines to get some idea that this drug may have some relevance.

I think an area that we probably need to do more work on is integration with new agents. I am going to choose leukemia as an example here. For those of you who don't do this on a regular basis, this, in one slide, is what childhood acute lymphoblastic leukemia therapy looks like with different phases of therapy from induction through consolidation, interim maintenance, all the way through maintenance to just over three years.

As you can see, in each of these phases we treat children with anywhere from six to eight different cytotoxics. Then, on this backbone of very successful therapy that is toxic and is not curing all children, along comes a new drug that has made its way through Phase I and Phase II and clearly has efficacy. The question is, is it going to improve outcome? The question is, aha, here is our new drug, and this drug in this case is the prodrug 506U, and now what? And "the now what" is not an easy question to answer. Where do you put it? What are the risks and benefits of putting it in any one place? We actually were confronting this problem, and still are with this drug as far as how do we integrate this into successful front-line therapy to ask a Phase III question?

Well, we have the advantage that 506U is actually a drug that is a very old drug that has only clinically come to our attention in the last decade. Work done by Trudy Allen many, many years ago, beginning in the '50s and extending through the '60s taught us a whole--and a number of other investigators. And, one thing that came to light with anti-metabolites was that there was a potential drug interaction, a negative interaction

with asparaginase. It turns out that for other drugs there is a very sequence-dependent drug interaction. So, we asked ourselves, okay, we are using asparaginase at a number of points in this therapy, is that a potential problem?

You can look in vitro and begin to get an answer to that. So, in this set of experiments we did sequential exposure. Nelarabine is 506U, so first exposing to nelarabine and then following with asparaginase, in this case, because this is in vitro and asparaginase is an enzyme, simply changing over to asparagine-deficient media and then asking the reverse sequence question at least in one cell line--and this is early work that is going to be presented at AACR in a couple of weeks, but in this case there is, indeed, a red flag. If you expose cells to asparaginase before you expose them to 506U you are going to have as much as a one log decrease in effectiveness. So, this is an important piece of information when it comes for us to try to determine what we should attempt to do and what we should avoid doing. This is far from comprehensive and, again, there are only two cell lines and one cell line really didn't have a significant effect. We have to do more work. But,

again, these models might help us in trying to understand how to integrate new agents on the backbone of effective therapy that we currently use in children.

I want to just share a few perspectives in closing. I will preface it by saying this was not a comprehensive talk on cell culture models and these are as much opinions as they are accepted fact.

In vitro models are a cost efficient method to search for activity, but mechanistic-based approaches likely will have a higher yield. In other words, drug discovery has moved on from screening I think in cell culture systems.

In vitro models can, however, further our understanding of drug action in pediatric tumors, and the moderate throughput is advantageous, especially when studying drug combinations. I showed you that for leukemia we treat with eight or nine drugs. It will become a nightmare trying to figure out all the combinations but with in vitro models you at least have a chance of grappling with some of the major issues there.

For most cytotoxic agents, if it does not

work in vitro it will not work in vivo. So, the negative predictive value for most cytotoxics is pretty good. If you can't kill the cell in the dish you probably shouldn't invest a lot of energy if this is a cytotoxic agent.

Correlated to that, if it takes a super-pharmacologic concentration in vitro to have an effect, it will likely not fare well in vivo. For the most part, you can kill cell cultures with anything if you put enough in so you do have to put it in the context of are these concentrations relevant concentrations.

Lastly, and this is where we probably fall down most often, if it works well in vitro there is a reasonable likelihood that it will do absolutely nothing in vivo. That is true of a lot of models and it is certainly true of cell culture models. So, I will stop there and let the program continue.

DR. SANTANA: Thank you, Peter. We have a few minutes for questions because we have to do two things, we have an open public hearing if anybody wants to speak and we also have to switch laptops. So, there is opportunity to address any questions to Dr. Adamson and Dr. Meltzer now. I have a question for Dr. Meltzer, you kind of hinted at the

end of your talk about an issue of peripheral blood and, I read in between the lines surrogate use of peripheral blood. Can you expand on what you meant? Did you mean that you would take the tumor diagnosis, establish a profile, and do it also with peripheral blood and diagnosis but then only monitor peripheral blood as your surrogate? Please go the microphone.

DR. MELTZER: What I really meant was monitoring toxicity, and the example that I know of that has the most effort is in actually monitoring for radiation toxicity. There are patients who are extremely sensitive to radiotherapy and have severe toxicity and there are some tantalizing preliminary data from Stanford that suggest that you can tell the hypersensitive patients by gene expression profiling of their peripheral blood. That is an approach that, to my knowledge, has not been really applied to chemotherapy and there may be an opportunity to do that. So, I was really speculating.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Peter, I think there are a couple of comments I want to make about what you said about the predictive value of these. One is

that I think there was a very interesting panel discussion at the AACR ERTC meeting in Boston this year about the predictive value of models in general. It wasn't just in vitro, it was talking about animal models. The conclusion was that they were basically non-predictive and, you know, no one had any magic models.

At the same time, when you look at the publication that is coming out of the NCI 60 cell line screen, what they are saying is that the one thing that was somewhat predictive is if they have activity in multiple different cell lines, then that tended to give you some predictive value. So, more is better in that setting.

The third is that there are some well-established principles that have been discussed in the literature and often ignored that say that if you really can get two logs worth of activity, whether it is in an animal model or in an in vitro model, that may be somewhat predictive. In other words, there is a two-log threshold, which you didn't address. And, I think when you talk about IC50s we clearly are not talking about multi-log assays or in the MPT system.

So, I guess what I am suggesting is that I

think that one reason why the predictive value of some of these has been less than we would all like is that, first of all, I think the systems still aren't optimized and I think they need to be done in multi-log systems and, secondly, as you pointed out, a number of us are studying things like physiological hypoxia and the impact on this. Certainly, as you pointed out very astutely, there must be consideration of what the pharmacological parameters you are going to see in a patient are when you approach these.

Third, I think what we really need is to be doing them in more cell lines, not just one, two or three but we need a lot of them. Once we get the right panels of biologic reagents in these systems and the right systems we might see the predictive value go up, and I don't think that we should exclude that possibility when we consider these.

DR. SANTANA: Dr. Grillo?

DR. GRILLO-LOPEZ: Another comment that I would like to make is that many of these models have been developed for chemotherapeutic agents and when you are dealing with a biological they may have no applicability whatsoever.

DR. SANTANA: Any other comments?

[No response]

We have a few minutes for an open public hearing so if there is anybody in the audience who wishes to address the committee, could you please come forward to the podium and identify yourself and any potential conflicts of interest, and make your statement?

Well, if nobody is going to take the opportunity, then we will invite Dr. Houghton to proceed with the next presentation.

Human Cell-Animal Xenografts: The Current Status, Potential and Limits of Informing us About Clinical Studies

DR. HOUGHTON: I would like to thank Steve for inviting me. When we were given the mandate or the subject of this afternoon's session, it was actually a clarifying moment to think about what sort of preclinical data is required or is of any use. I think there are two ways of looking at what sort of preclinical data can be of use. That is, use for us in sort of designing clinical trials as opposed to perhaps the information that would be required for the FDA to make some sort of decisions regarding the potential use of an agent.

So, I think we can look at early drug discovery largely within defined standardized environments, either in drug discovery groups within companies where you have set protocols and set criteria for establishing whether an entity has adequate activity to progress to the next stage, or in the NCI screening program where, again, there is a set of protocols that drive the criteria for advancement of the compound. The problem is that pediatric cancers are represented in neither entity. They are obviously not going to be a focus of the pharmaceutical industry and, as Peter alluded to, despite multiple attempts they were not included in the NCI screening program.

The consequences of preclinical data using pediatric models is generated essentially in an uncontrolled or non-regulated environment where everyone uses their own pet models, their pet design of experiments and, in fact, their own criteria for assessing whether or not they regard something as being active. So, such data derived from experimental systems that are not validated, using experimental designs that are, again, not validated and interpretation of those results lacks consistency and rigor.

So, taking advantage of the approaches that have been taken in industry and the idea of developing a consistent, criteria-driven approach a group, many of whom are represented here, under the leadership of Malcolm Smith, Barry Anderson and Peter Adamson, met during 2002 to consider what sort of screening program would be useful to implement that would allow us to identify drugs that are in the early clinical or just at the late preclinical stages from industry that might be useful in identifying drugs that would have specific application and perhaps should be prioritized for pediatric clinical testing.

The schema is shown here and I am not going to go into detail on this because Malcolm is going to deal with this in somewhat more detail in his talk. But the idea is to set up a panel of models so tumor A may be medulloblastomas and tumor B may be neuroblastomas, a panel of six to ten of these comprising either xenografts or heterografts of human cancers in immune incompetent mice, or where there are transgenic models to implement those within the screening program. But the idea would be that we would have a framework where we can set the criteria for experimental design, set

the criteria for assessing responses that may be more consistent and may generate data that would be of use not only to us as a group that are interested in developing clinical trials, but perhaps more appropriate use to a federal agency such as the FDA if they wanted to use such preclinical data.

So, we were asked to look at the following categories of nonclinical data, and I am going to concentrate on pharmacology and pharmacokinetics efficacy and the aspect of using the models to identify pharmacodynamic endpoints that may be more amenable to analysis within the model systems than they are, certainly, in patients with solid tumors. The other aspect is to ask where such data fits in terms of development of drugs in the pediatric cancer realm.

I think the models can be useful in identifying active agents and perhaps better analogs to optimize the administration schedules, or to look at drug combinations in vivo, to prioritize agents for Phase I trials, to make rational decisions within the pediatric consortia as to whether to continue to develop drugs or whether, at some point, we should drop those drugs

in further development, preferably at the Phase I to Phase II transition to allow us to potentially focus a drug in treatment of certain tumors for the specific activity against certain models in the pediatric clinical screening program, and the potential to relate target inhibition to biological response which is going to become progressively more important as we deal with more agents that are inhibitors of specific signaling pathways.

So, the data that suggests that some of these preclinical models may be useful is shown here. This is from rhabdomyosarcoma models, and this is data that was gathered over about a 10-12 year period in my own lab which identified vincristine, cytoxan, dactinomycin D and Adriamycin as having good activity against panels of rhabdomyosarcoma xenografts. On the right column are sort of the response rates that have been gleaned from the literature that was available.

On the other hand, it shows on the bottom that norfolan is a very active agent in the preclinical models and, indeed, is very active in rhabdomyosarcomas. However, there is a cautionary note here. Although we can identify drugs that are active in model systems and potentially active in

the clinical setting, it doesn't necessarily mean that this is going to be a good drug. The limitation of norfolan is that it causes cumulative toxicity to bone marrow and subsequently limits the ability to deliver standard therapy to those children.

So, we have to look at these results as being promising in terms of being able to retrospectively identify drugs that we know are active in the clinical setting and to prospectively identify drugs that may have activity. That doesn't necessarily mean to say that that drug is going to be potentially a very useful drug in the clinical setting. So, there is a limitation to the models even though they are very promising. Ultimately, the value of the entity itself has to be determined in clinical trials. We can merely point in that direction.

On the other hand, you can take the same drugs and run those against colorectal adenocarcinoma xenografts, again, in immunodeficient mice and you see that the drugs that are very active against pediatric rhabdomyosarcoma essentially have no activity against the colon xenografts. So, that gives you a

little bit more confidence that it is not the fact that you have heterografted a tumor into a mouse that dictates its response.

Coming to some more recent data, we have established a series of Wilms tumor xenografts, WT1 through WT10, favorable histology Wilms tumors, and SKNEP is a cell line that was derived from a diffused xenoplastic Wilms tumor and the more pluses there are, the more sensitive the tumor is. So, anything that is greater than a 4-plus is an objective response in this model, so 50 percent regression in tumor size.

So, you can see with vincristine, WT1 through WT10, is 6-pluses which means that these tumors completely regress and do not regrow within a 12-week period of time. Similarly, cytoxan has very good activity in most of the tumors. Prospectively, the model identifies the camphotecan, topotecan and irinotecan as being very active. The important thing here is that topotecan and irinotecan are administered at doses that give relevant systemic exposures to humans.

The relative exposure is perhaps the most important change in the way we are thinking about how to look at efficacy. Efficacy in animal models

is defined as the anti-tumor effect, let's say the ability of a drug to inhibit growth by 50 percent, divided by the dose that causes 10 percent lethality. The problem is that the mouse is not a very good model for human toxicity. The mouse may be either less tolerant to a drug, in which case you may under-predict the activity against a human tumor, or may be much more tolerant than a human, in which case the drug looks fantastic against the heterograft but ultimately fails in the clinic because you can't achieve systemic exposures in the patient that are consistent with the tumor regression in the mouse.

The data shown here is the responses of different neuroblastoma xenografts to the drug topotecan against systemic exposure or area under the curve in nanograms per milliliter, showing that if we target, where the arrow is, 100 ng/ml we would expect to get in this case four out of the five tumor lines to give some response. In fact, the total data set was the sixth line which is also completely resistant to topotecan. So, we would predict if we targeted 100 ng/ml that we would have a response rate of four out of six or around 60 percent.

These sort of data are interesting but ultimately you have to prove or validate that this approach does have some merit. That has been done in a clinical trial that was headed by Victor Santana, and the pharmacokinetics was done by Clinton Stuart, at St. Jude. The idea here was to target the same systemic exposure that we set in the mouse, the 100 ng/ml of topotecan-lactone, and the design of the clinical trial is shown at the bottom.

The drug is given for five days on two consecutive weeks, which is the schedule that is most effective in the xenograft models, and on day one there are pharmacokinetics taken and then the dose is adjusted to hit this target dose. We are getting quite good at doing this. In this particular trial there were 113 courses of drug administered and 92 percent were in the 100-plus or minus-20 ng/ml range.

The results are shown here, where for 28 evaluable patients we had approximately a 60 percent response rate which is very close to that which would be predicted from a limited number of xenograft models, again suggesting that the idea of using pharmacokinetics as the metric against which

anti-tumor activity is measured is perhaps more appropriate than using mouse toxicity per se.

We looked at the retrospective analysis, again, about ten years work, and we see that for drugs that really didn't progress from Phase I any further, the area under the curve at the mouse maximum tolerated dose versus that in the human is somewhat higher in the mouse than the human. So, in this example, the mouse is about 80 times more tolerant than are humans. Yet, when one looks at the effective dose range, the effective dose range being reductions from the maximum tolerated dose in the mouse at which point you lose objective regressions in your tumor models, we see that the effective dose range for these drugs is relatively small, between two and three.

So, where you have such discrepancy in the tolerance between the species and, yet, a very narrow window of true activity against the model systems which are human, one would anticipate these drugs would not necessarily achieve adequate concentrations to give tumor responses in a clinical situation.

Drugs that work are shown here. Norfolan, despite its limitations, is very active and, again,

the pharmacokinetics in the mouse and the human in terms of tolerance are very similar. There is a reasonable dose range of three to four before you lose activity. Similarly, for topotecan the effective dose range spans the differential between mouse and human, as does irinotecan which is very well tolerated in terms of the active metabolite in the mouse and has an extremely wide therapeutic range within this model system.

Looking at a more recent drug, irofulvin, NGAI114, again, anything that is more than a 4-plus is causing objective regressions. We have looked at some 18 models. It looks very active. If you dose reduce you see that the MMT is somewhere between 4 and 7. So, let's say you have 14 out of 18 tumors, independent tumors show activity in terms of objective regressions. As we reduce the dose further, it is 8 out of 18; reduce the dose further, it is 3 out of 15; and the lowest dose evaluated, only 1 out of 14 different tumors showed objective regressions. These include tumors derived from brain tumors, neuroblastoma and rhabdomyosarcoma.

The problem here is that even at this dose the systemic exposure to this drug in the mouse

exceeds ten-fold that which can be achieved in human trials, again, suggesting that here is a drug that looks dramatically active in a model system but when you relate that activity to the ability to achieve systemic exposures of the drug in human it would suggest that this is a drug that would not be of high priority to undertake clinical trials, or at least progress from Phase I to Phase II clinical trials.

Similarly, I think we can address issues of schedule-dependent anti-tumor activity. This is old data with topotecan, but topotecan is given for 5 days for every 21 days over 3 cycles, or given for 5 days times 2, so it is Monday through Friday; Monday through Friday at half the dose. So the cumulative dose in both of these trials is exactly the same but the outcome in terms of tumor response is very different.

I think this sort of data, where it is derived in a substantial number of tumor models to show that this is a consistent finding, may also be quite valuable in leading us in the design of clinical trials especially where, as was mentioned earlier today, one tends to get one shot at doing a large clinical trial and we might as well give it

the best chance we can.

The other aspect is the discrimination analogs of a particular class of chemical. I think the models again can be quite useful if you apply this in the context of the achievable systemic exposures in humans versus the mouse. This shows some data from an osteosarcoma xenograft which is particularly sensitive to carboplatin and cisplatinum but oxaliplatin, which is a drug that is of current interest in the pediatric oncology world, shows essentially no activity. I think if one extends this data to, say, 6-10 osteosarcoma models and sees that, in fact, oxaliplatin has very little or no activity against these models, this can be factored into how we develop this drug in the clinical setting.

These are classical cytotoxic drugs and, obviously, over the next few years there is going to be a progressive shift to drugs that we fondly call molecularly targeted drugs, even though perhaps they aren't quite as specific as we think they are. But under those conditions we have to generate models that very accurately recapitulate the activity of, for example, signaling transduction pathways. This raises the question of

whether the conventional subcutaneous model is, in fact, going to be useful or whether we will have to go to models where the tumor is implanted into the more physiologically relevant sites, such as brain tumors into the brain, Wilms tumors into the kidney, etc.

One way of addressing whether this is the case or not is through expression profiling and proteomics profiling, as alluded to by Paul Meltzer. We have been looking at nearly established models and I will show you a couple of examples here where we have looked at Wilms tumors when we transplanted them into mice as xenografts and have done profiling from the primary tumor from which this xenograft was derived and the xenograft.

So, what we are looking at here is the expression profiles for about 6,000 genes that are expressed at reasonable levels in the xenograft versus the primary tumor. As you can see, there is a very high level of concordance, with about 20-30 genes that are expressed greater than one standard deviation from the mean. The data suggests very strongly that the expression profiles that are observed in the primary tumor are very largely recapitulated in the early xenograft studies.

This means two things. It gives us the first real metric to say this model is representative of the parental tumor because previously we have looked at histology and maybe measured a few antigens to see whether they are retained or not. Now we can do this by profiling 25,000 to 30,000 genes.

Then having this data set, we can do two things. One is, as these tumors are serially passaged in mice, from one mouse to another, we can ask a very pertinent question, at what point do these models start to deviate from the original tumor and, thus, may have much less relevance, particularly for screening or evaluating activity of molecularly targeted drugs.

The second use is that if you have really consistent profiles like this, and these are maintained for multiple generations in the mouse, then we have the ability to look at the effects of drugs to perturb these profiles and start to get molecular signatures that may relate to biological outcome, that is, tumor response.

One of the uses that we have made of this data is in collaboration with GlaxoSmithKline in cytokinetics, who had data, shown here, that the

gene for the mitotic KSP was expressed at relatively high levels in tumors and particularly in Wilms tumor. So, the arrow shows the levels of expression in normal kidney, which is extremely low, and also in clear cell carcinoma of the kidney and transitional cell carcinoma the expression of KSP is very low, but in Wilms tumor, which is circled here, it is extremely high.

It allowed us to ask the question whether high levels of expression of KSP did, in fact, make this a drug target. We have looked at one of the analogs of an anti-kinase inhibitor that is an analog of the compound that is currently in the clinic, and we have looked at this against a panel of Wilms tumors. The bottom line is that this is a very active agent against favorable histology Wilms tumors that over-express KSP. It is, unfortunately, not particularly useful against the diffuse anaplastic variety, here. That is based upon a single xenograft and we are trying to establish further models and will see if that is, in fact, the case.

In terms of the anti-tumor activity, if we can just focus here, this is tumor volume versus time after starting treatment. Control is here.

This is the KSP inhibitor inducing complete regressions, with only 2 out of the 5 tumors regrowing during the 12-week period of observation.

The limitation of this particular analog is that whilst it works very well at the highest dose, there is a very steep dose-response curve and there are much less active fractions of the MTD. So, again, this is going to be a drug where the relative pharmacokinetics between the mouse and the human are going to be really quite critical in determining whether this is very likely to have therapeutic benefit in these tumors.

The final part of this is really this aspect of pharmacodynamics. As all of us know, to look at target inhibition and, more specifically, target inhibition and target recovery in patients with solid tumors has been, and will remain to be, a very difficult proposition. Multiple biopsies of tumor at various times before and after treatment is in most cases not really possible.

I think the models can be quite useful in this respect and I will illustrate that in terms of the signaling pathway that we will be looking at in the context of a therapeutic trial of a rapamycin analog, CCI779. This particular analog targets

serene kinase, and it is very easy to monitor the effect of this drug by looking at downstream effectors and whether they are phosphorylated downstream.

The problem is that target inhibition is only the first part of the question that you really want to ask. That is, you are really asking at the drug doses that I am giving am I inhibiting the target? That is the first part. But what you really want to know is does the inhibition of target correlate with biologic readout.

I think the model systems are going to be very useful to link the pharmacokinetics to target inhibition to biological readout in terms of anti-tumor activity, but even more so in terms of developing concepts of molecular signatures that may be much more important in predicting the outcome for treatment than merely looking at the target inhibition per se.

Malcolm Smith will discuss this but the developing initiatives at the NCI include to systematically characterize tumors at the molecular level using both genomic and proteomic arrays. The second is the Pediatric Preclinical Testing Program where we hope to establish models to identify new

active drugs.

I think in terms of using preclinical or nonclinical data we have to standardize our experimental procedures. This is going to be difficult, but in the context of the proposed consortium that I have described it is difficult but it is a realistic goal, and I think once we have a group that is doing this on a large scale under consistent conditions, then I think others outside of that consortium who are doing similar work may adopt the same criteria for looking at tumor response and the design of experiments so that their data and our data can be compared and normalized. I think we have to be careful that we use standardized criteria for assessing drug activity and, again, I think this is something that will come out of the consortium or the PPTP initiative, whoever carries that out.

One of the other questions that was being raised is should we be using animal data that is derived under Good Laboratory Practice compliance. The problem here is that if we do this for the cancer screening program, then my understanding is that the entire vivarium within an institute or university also has to function under GLP

conditions and this aspect of the work may be a very small percentage of the total work that is being done in a vivarium per se. It would certainly increase the costs quite dramatically so I think we have to think about the prospect of GLP in the context of who is going to be doing this work and whether this would increase the cost of animal experimentation not only for the work that is being focused on cancer, but also for non-cancer related work that is ongoing in the same institution. Thank you.

DR. SANTANA: Thank you, Peter for a very thorough overview of this issue. I am going to ask Chand Khanna to go ahead and do his presentation. After that we will take a break and then we will come back and reconvene and finish the last two presentations and have our discussion and questions.

An Integrated and Comparative Approach to Preclinical/Clinical Drug Development

DR. KHANNA: I want to thank everyone for the opportunity, specifically Steven, to come and speak to you today.

As Peter suggested, the convention to drug development, as you all know, is to include

preclinical models to evaluate promising agents and then move those promising agents through clinical development. To continue Peter's theme, what I would like to present is a vision towards an integrated approach wherein preclinical models can be helpful and informative, both at the preclinical level and during various phases of clinical development, and the spin that I would like to provide is one that includes a number of novel models, models that have not been used very much in drug development, and those include naturally occurring cancers that are seen in both genetically engineered mice and, more specifically, in pet animals in our communities that can, again, be included in translational and biological cancer research.

What I am going to do is to bring this to you from my efforts within the Comparative Oncology Program of the CNI, which is a new initiative within the Center for Cancer Research, and my work with the Pediatric Oncology Branch where my focus is on sarcoma biology and metastasis.

As Peter has alluded to, there are a number of modeling options, and the ones he has focused on and shown us really are how we can best

use the xenograft models, but there are also opportunities for us to include syngeneic or mouse cancers that are transplantable into mice, and genetically engineered mice that can be used for a number of important steps in the translational process. Lastly, what I want to focus on is the use of pet animals in the drug development process.

This is a schema that you are familiar with, wherein small animals are used early in the development. Primarily for toxicology we use large animals, whether they be non-human primates or dogs, and then we move into clinical development. The question is how can we use first a small set of examples genetically engineered mice to inform this process? Largely, I think, because they are more complicated and challenging, we can use them in the evaluation of interesting findings from traditional transplantation models.

So, if we look at the historical perspective, genetically engineered mice have been problematic for basically three primary reasons: One is that they are conventionally associated with very rapid tumor progression. They are historically associated with hemologic malignancies and the cancers that emerge usually emerge in a

number of sites synchronously.

Recently there have been novel modeling approaches which have provided us an opportunity to study genetically engineered mice across a range of cancer histologies, almost all histologies. Through efforts including conditional expression of genes, somatic expression of genes within a selected pool of target cells, there are now very good mouse models for most human cancers. The advantages that these genetically engineered mice provide through the translational process are that after you induce the genetic change in the mouse the cancers that emerge, emerge spontaneously. That is one.

The second is that the tumor that emerges is syngeneic from the tumor to the tumor micro-environment to the host, and that is something that I think provides opportunities specifically for targeted biology-based therapies. The genetics of the cancer are modifiable and are relevant and, although it is more easily said than done, the biology of these cancers can be controlled now so we can have opportunities for therapeutic evaluation during the course of progression that these genetically engineered mice

have.

There are limitations, and the limitations that we see with traditional animals still exist with these genetically engineered mice. There is heterogeneity within a specific population of mice. There is heterogeneity in the genetics of the cancer and I think that is a value. It adds to what we get out of more or less homogeneous populations seen in the transplantation settings. Experimentally, these are very difficult and complicated designs to pursue from the standpoint of translation but they can be done. They are expensive, time consuming, and we don't really know yet about their predictivity.

The most important issue about their use is a series of patents that have been provided to Dupont exclusively that really extend to all genetically engineered mice. Any activated oncogene in a mouse is covered by the OncoMouse patents. The result of these patents is really the limitation of their use in the pharmaceutical industry. So, unless this issue can be dealt with, I think the use of these genetically engineered mice in the pharmaceutical industry will be limited.

What I want to move on to is ways for us to include naturally occurring cancers in the translational process in the drug development process. Again, within the Comparative Oncology Program what we plan to provide are opportunities to include these models in drug development. So, pet animals have a number of interesting cancers that are relevant from the standpoint of pediatric cancers, including lymphoma and then dogs with osteogenic sarcoma.

Dogs in the community are developing these cancers. There are 65 million pet dogs in the United States, 6 million will develop cancer in a year and the pet owners of these dogs are seeking out advanced care and, in many cases, are very interested in including their dogs in trials that evaluate new therapies. So, what this provides is an opportunity to include these large animal models in drug development and this has been done largely within the pharmaceutical industry.

The advantage that these large animals provide is, in fact, that they are large outbred animals, unlike the small animals that we traditionally use at the preclinical level. The genetics of the host, the dogs, have been shown by

the recent completion of the canine genome to be quite similar, very similar in fact, to humans. They are naturally occurring cancers. Then, within given histologies the genetics of the cancers are very similar to the genetics of the same human cancers. Very importantly, one thing that these models provide is that within a histology there is considerable genetic and individual variability that is, in fact, captured within populations of humans and often is the problem as we move through clinical development. This heterogeneity is not captured in other models.

If you look at histology responses, for example lymphoma, the drugs that are effective in dogs with lymphoma are effective in people with lymphoma. The drugs that are not effective in dogs with lymphoma are not effective in people with lymphoma. To a large extent, that parallel is true for a number of histologies with classical, conventional cytotoxic drugs. The biology of metastases within these models is faithfully reproduced for specific histologies. Lastly, I think an important point is that these cancers are characterized by resistance or recurrence and this is really the problem that we face with pediatric

patients and adult patients. The biology of recurrence or resistance is difficult to model in most small animal settings.

So, if we look at this table that I have taken from Shadner's recent review in JCO, he has listed out preclinical through clinical development of the number of agents at various phases at one point in time. What I have done in red is just put the number of agents that are active per year. By looking at this, you can see where opportunities exist to improve the process of drug development. Certainly as Peter suggested, there is room for us to improve this initial step but as we move along, I think there are great opportunities for us to take Phase I agents that are not burdened by the hurdle of maximally tolerated dose and inform decisions towards Phase II. I think there is an opportunity for these large animal models, for genetically engineered mice to take that role of informing towards Phase II and potentially informing towards Phase III.

So, this is the integrated approach that I would like to suggest wherein pet dogs--we have largely done this work within the pharmaceutical industry to assess activity, toxicity,

pharmacokinetics and pharmacodynamics and used that information to lead towards Phase I. Well, perhaps as important, use these tumor-bearing dog studies to define dose regimen schedules towards Phase II to validate, potentially to identify but really more appropriately validate biomarkers, define responding histologies, and then provide a rational system in which we can demonstrate that combinations should be considered towards Phase II and potentially Phase III.

So, I would like to give you a couple of short examples. Thrombospondin-1 is a very large protein with a number of receptors and a number of effector domains. The second type-1 repeat has been associated with significant antiangiogenic activity. From the second type-1 repeat a series of small peptides, non-amino acid peptides, are being pursued as anti-cancer drugs, antiangiogenic drugs. The problem with the development of this class of drugs and specifically thrombospondin-1 is that although we can show within mice that these agents are antiangiogenic and although we can show that they do have anti-cancer activity, the leap towards the clinic has been difficult.

So, the question was whether or not we

could use dogs with naturally occurring cancers to help us make that step. What I would like to show you is a simple example of how we have done that. The experimental clinical trial for pet dogs included dogs with any measurable malignant cancer, no concurrent therapy, and the endpoints really were to assess toxicity, a limited attempt to evaluate PK, and then to look at response, keeping in mind that response was going to be assessed against bulky disease using a single-agent antiangiogenic drug.

The first point that I want to bring up is that accrual is achievable. In a short period of time we can enter large numbers of dogs in these clinical trials with the support and interest of their pet owners. Toxicity has always been evaluated, in fact, in dogs. An interesting and important point is that pet dogs that bear cancer have different toxicity profiles than beagle dogs that are evaluated in the research setting. In fact, in many situations the toxicities that are seen in pet dogs are much more similar to those toxicities seen in patient populations.

I will show you some of the responses. This is a dog with a maxillary squamous cell

carcinoma. This is the lesion after 30 days on therapy. It is perhaps a little clearer here. After 60 days the lesion is much more active. It is hemorrhagic. Through a 60-day period of time in a human clinical trial, Phase I trial, it is unlikely that you would continue this patient on therapy with progression. But we did continue this dog and after 90 days, the lesion is now no longer present. We can biopsy this site and there is squamous cell carcinoma that is persistent there but the lesion is not actually assessable there. So, this dog continues to do well, free of disease that is measurable within the mouth, but not a histological regression.

I have several other images that I could show you to suggest, in fact, that the agents are active and they can result in regressions. The responses include stabilization which we feel are real but, in fact, objective regressions of lesions that cross a number of histologies.

The other thing that this points to is, in fact, histologies that we wouldn't have predicted activity in. So, lymphoma was found to be quite an active site and now, in Phase II, these drugs are moving ahead. Of interest to the group, sarcomas

were particularly responsive histology.

So, what did we learn from these dog studies? Antiangiogenic peptides can be active against bulky disease. They need time. Because of the results that we were able to generate in dogs, the Phase I trials in Europe extended their observation times and they did see objective responses in patients treated for 60 days.

Agents are active against histologies we wouldn't have predicted, like non-Hodgkin's lymphoma. A very important point is that all dogs that continue through therapy develop resistance on therapy so combinations are going to be necessary and, as we look towards the use of these agents, we are going to have to keep in mind that resistance will be an obvious problem. Most dogs don't respond to therapy and, therefore, there is an opportunity for us to define markers that predict responsiveness within a heterogeneous population of dogs and, in fact, predict when responses will be seen. That work is being done and thus far circulating endothelial cells seem to an interest and will move on into the clinical setting as well.

This is, again, the perspective that we have and I think there are some examples from the

thrombospondin-1 studies that show how we can inform towards Phase II. I want to end with another brief example and it speaks to this pharmacokinetic/pharmacodynamic response question that Peter brought up.

So, Cheryl London, who is at UC Davis, is evaluating small molecule inhibitors of the split tyrosine kinase receptor family. What she was able to do in a very similar trial design, treating dogs with bulky disease, is actually do tumor pharmacodynamics using phospyl KiT as the target; do serial biopsies in dogs evaluating the diversity of KiT mutations in dogs with nasal tumors and define the dose that is required to modulate the target in vivo to validate surrogates that could be more evaluated in human clinical populations against this tumor target, and then move those things into the clinic.

She was able to show that the dosing schedule, an every other day dosing schedule, was valuable and able to achieve threshold receptor inhibition of KiT. This information was translated directly into the development of products in clinical trials. The every other day dose was suggested for human development but the human

development required input from marketing and marketing didn't want to pursue every other day dosing. The drug trials predicted daily dosing would be toxic and, in fact, was toxic in people.

I am just going to jump ahead. So, what we are interested in being able to do within the Comparative Oncology Program is provide a reagent kit that can allow biology-based questions to be answered in these trials. This has been a difficulty for dog trials thus far in that we just don't have reagents to study dogs in a rigorous way. We now have a validated canine oligoarray, a 17K element array. We are validating proteomics approaches in dogs with cell signaling. We have screened specific antibodies for cross-reactivity to dogs and we have made good progress there.

Multicenter collaborations are going to be required for us to be able to do trials in a short period of time, and allow that short period of time to inform towards clinical development of the same drugs, and to be able to help with decisions of when these models can be used and when they should not be used in development. There are times where really the questions are not appropriate to ask within these dog studies.

I will just end with a list of histologies that I think are relevant. Osteosarcoma is obviously an area of personal interest and we have actually published randomized, prospective, placebo-blinded trials in dogs with osteosarcoma looking for opportunities in the clinic.

We are interested in lymphoma. There are other histologies. But important to note is that within each of these cancer histologies are genetic changes that can be modeled and can be targeted. So, it doesn't have to be histology based.

The weaknesses of these models are the cost. Drug costs are a primary concern; the cost of managing the trials and time. They are longer models than what we would see with typical small animal studies although the time is much shorter than what you would have in the same clinical study in a human population.

With that, I will conclude. I will acknowledge our initial group in Comparative Oncology, and the slide also includes Lee Helman and the people in the Pediatric Oncology Branch. UC Davis and Cheryl London has been doing a lot of these translational studies. Now, with the interest of CTEP and the CCR, we are pursuing some

trials with 17DMAG to answer some of these questions that will inform towards Phase II.

DR. SANTANA: Thank you, Chand. I will seek the advice of the FDA. Should we take a ten-minute break and try to get back on schedule because I know we are going to have people dropping off as the day progresses. So, why don't we just take a ten-minute break and reconvene at 3:00, finish with the two presentations and then take questions and discussion and try to get out of here on time?

[Brief recess]

DR. SANTANA: I will invite our next speaker to come to the podium. Dr. Kenneth Hastings will address the issues of what can be learned about safety using different models.

What can Learned About Safety?

DR. HASTINGS: Well, my task, after these really nice scientific presentations, is to give you the regulatory spin on things so your task is to stay awake.

What I want to talk about today is the use of neonatal and juvenile animal studies for determining the safety of drugs for use in pediatric patients and, obviously, this is going to

apply to pediatric oncology.

The specific guidance that really led to the development of guidance on juvenile animal studies was the Pediatric Exclusivity Act under Section 505A of the FDC Act. The specific language that is included that refers to nonclinical studies is that the FDA may request nonclinical trials before completing pediatric studies in humans. Certain toxicology studies in immature animals may be necessary to evaluate the safety of use in pediatric conditions.

Also another regulatory background document has been referred to previously, and that is ICH E11, clinical investigation of medicinal products in the pediatric population, and once again the decision to proceed with a pediatric development program involves consideration of many factors, including any nonclinical safety issues. The need for juvenile animal studies should be considered on a case-by-case basis. Then it refers to ICH M3, which is the document that outlines the timing of nonclinical studies vis-a-vis clinical studies.

Finally, there is a draft document that was published in February, 2003, nonclinical safety

evaluation of pediatric drug products. We now have the final version, after comments were made to the docket, and we hope to publish it sometime this spring or summer, and we took into consideration the comments that were made. This document provides guidance on the role and timing of animal studies in the safety evaluation of therapeutics intended for the treatment of pediatric patients, and it also provides specific recommendations based on the available science and pragmatic considerations.

Why did we get into the issue of juvenile animal studies? Well, in assessing the use of drugs for pediatric use the basic assumption that we have proceeded with over the years has been that under most circumstances the safety and efficacy of drugs approved for use in adults predicts pediatric use if you make the appropriate dose adjustment.

Now, in the past we have used things like relative body surface area. We consider that to be a good default measure for dose adjustment. But generally this is less informative than data you would get from a clinical pharmacology study. That is really what we are after, being able to make dose recommendations based on actual ADME

pharmacokinetic studies.

Neonatal and juvenile animal studies to enable clinical studies are needed basically to support the safety of studies in pediatric patients. The origin of the guidance really was to provide information and what we call triggers on the need for nonclinical studies. Basically, what we are saying here is that you don't need to do a juvenile animal study every time you want to do a clinical trial in a pediatric patient population. What we were trying to do is to find out what are the sorts of things that we could observe or already know about the toxicology or the safety of a drug that would tell us that maybe you need to do a pediatric juvenile animal study to support the safety of a pediatric study.

Also, this guidance contains advice on the conduct of the studies and provides information on how the results of these studies would be used in designing pediatric drug trials and, in fact, in deciding whether or not they would be safe.

Now, we recognize that there are differences in the drug safety profiles between mature and immature systems, and these include differences in susceptibility to insult and

differences in toxicity-related ADME parameters. We recognize that some physiological systems are more vulnerable than others, especially those that undergo extensive postnatal development.

When you think about it, you know, that doesn't exclude much. There are a lot of things that undergo significant postnatal development. So, really more than anything else what we would think about are those that might be particularly susceptible to insult, such as the developing nervous system, maybe the developing immune system, the kidneys, perhaps even the gut. So, those would be potential triggers for asking for a juvenile animal study if we knew from adults, from clinical practice or from mature animal studies, that these are target organs of toxicity.

Now, I want you to keep in mind two basic concepts that toxicologists use all the time. They have to do with how you look at the usefulness of studies, what it is that you intend to get out of the study. Actually, I have them in reverse order. The first are studies that are designed for hazard identification. Basically, the idea behind hazard identification is that you demonstrate that a drug or a candidate drug has the potential to cause an

adverse effect. An example of hazard identification would be something like an Ames assay or a discovery toxicology study where you administer a drug by intraperitoneal injection. You are just trying to find out if a drug can cause a toxicity.

Pertinent to our discussion today, under certain circumstances adverse effects in mature animals might not be predictive of adverse effects in developing systems. So, some studies that you might conduct, some juvenile animal studies you might conduct actually might be for the purposes of hazard identification, and I am going to talk about how that plays into the design of studies a little bit later.

Risk assessment, of course, is that you are trying to look at all of the parameters of toxicity--systemic exposure, route of administration, length of exposure, all of the parameters that determine whether or not what is a potential toxicity is actually going to be manifest as a toxicity in the use of the drug. Basically, this is one of the assumptions that we make when we say that for studies conducted in mature animals the effects will predict what happens in neonates.

What you need to do is determine what parameters, particularly ADME parameters might alter that risk.

I want to just mention very briefly the differences in pediatric versus adult patients or subjects with respect to ADME because that really was the driving factor in looking at juvenile animal studies to start out with. In humans, if you look at ADME, there are differences with age as far as distribution of drug dose. The receptors come and go; they develop and certain age-restricted ranges and, therefore, what you observe in younger systems may not be applicable to older animals and, obviously, extrapolating this clinically.

As far as absorption of an orally administered drug, you have to consider that in infants they have a larger volume of distribution, larger surface area to body weight ratio, and the body composition is different. Infants and children have higher gastric pH which will affect the absorption of basic and acidic drugs, larger absorption of the basic drugs; less absorption of acidic drugs. GI motility is different. In infants and neonates GI motility tends to be fairly low compared to adults. In children the motility

tends to be high compared to adults. So, the actual achievable AUC for a particular orally administered drug may be different if you just do your extrapolation based on body surface area. And, there are certain other things to consider, such as unique routes of exposure such as through mother's milk.

A very difficult issue is metabolism. We know that as a general rule there are certain metabolic systems that appear to be more functional in pediatric patients versus adults. I am not going to get into a long discussion about differences in metabolism except to say this, with respect to P450 enzymes, if you look at juvenile animals and if you look particularly at rats which is a model that we use quite often, we actually don't know a lot about the relative development of the P450 enzymes. There is probably one exception to that. We thought that there would probably be a lot of information on this. It turns out that actually there is not in the published literature.

Finally, another thing to consider is excretion in juvenile animals--actually, I am talking clinically but in children you have lower glomerular filtration rate, lower tubular

secretion, resulting in slower clearance and longer half-life. Once you get up into the child range you have rapid clearance and shorter half-lives. So, once again, pharmacokinetics may not be predictable based on body surface area.

One thing to consider is how valuable are animal models for ADME comparisons. Well, an obvious advantage is that in animals you can do experimental manipulations that might help you define ADME parameters. But a not so obvious advantage, as I have mentioned, is the lack of comparative information in animals, particularly with respect to metabolizing enzymes. One thing to consider though is that if you can associate PK parameters with adverse effects in animals, this might be useful in clinical trials. So, that is one real advantage to a juvenile animal model.

Really ADME was what originally drove the consideration of doing juvenile animal studies. Obviously, the other thing that we are interested in is toxicity. Are these studies going to be safe? The things that we need to consider are the relative maturations of physiologic systems. These are probably better understood in animals but we could have a debate about that. If adverse effects

are observed in mature animals, then the juvenile animals could be used to demonstrate increased or decreased susceptibility, and you may be able to understand how ADME might affect that. Once again, however, extrapolation to clinical trials may be less certain because of the variations in, for instance, metabolism that we don't really understand as well as we should in animals.

Let me lay out a couple of scenarios where juvenile animal studies might be useful for the purposes of toxicology studies. One thing, you may need a juvenile animal study if you already have a pretty good handle on the adverse effects and you have a pretty good idea about the ratio of toxic dose to efficacious dose, and particularly this may be true for short-term use drugs like antibiotics.

However, and this was mentioned earlier--I believe Dr. Santana mentioned this, sometimes even with acute exposure you might need long-term follow-up studies. The classic example for this is the fluoroquinolones. What happened here, as you probably are aware, fluoroquinolones are associated with a very troubling effect called crippling arthropathy. It was originally discovered or described in puppies, in young dogs. The question

was the clinical relevance of these studies. There is a lot of talk about this and I don't want to get into that debate but I think that most people nowadays consider that fluoroquinolone use in children is something you approach very carefully because this may very well be a serious adverse effect that would persist into adulthood.

One of the ways that we have looked at answering this question was simply to do this, to dose juvenile dogs, beagles, with fluoroquinolones over a course of, like, two weeks at, say, doses equivalent or maybe higher than what you would use clinically, producing AUCs equivalent to higher than clinical doses, and then just let the dogs go, let them mature and then, at about six months of age, you would look at the dogs again and do clinical evaluations, to histopath on the affected bones and see if there are any changes in those animals; see if the effect gets worse; see if it improves; see if there are any associated lesions that appear to be caused by this juvenile exposure.

In fact, what we now know about fluoroquinolones--to cut to the chase--is that actually these effects tend to persist. They probably don't get worse but they do persist. That

is an important thing to learn in deciding whether or not to conduct a clinical trial, let's say, for something like otitis media, and also to look at the follow-up. In fact, that was used as an argument for the long-term follow-up of children in clinical trials with fluoroquinolones, and I think this is something you should take into consideration when you think about oncolytics used in pediatric patients. I think it is a pretty good comparison that you might want to think about.

When you talk about long-term use, particularly, let's say, a drug that has never been developed for use in adults, then you might think about what we would call a shift to a hazard identification type of study. What you would do here is you would start with juvenile animals. You would dose them all the way through adulthood, look for adverse effects and then, if you do see adverse effects, you can go back and do window of vulnerability studies where you try to find out where, in the development of that animal, this occurred and this could help you in understanding where the vulnerable windows would be in a clinical trial. In other words, you can build risk assessment into what is in fact, when you think

about it conceptually, a hazard identification kind of study. You can also build in pharmacokinetics, obviously, and safety pharmacology studies such as effects on blood pressure, cardiac function, renal function and things like that.

I just want to make one mention about efficacy models. We have had a lot of talk about efficacy models; very good talks. I just want to say that you can build safety determinations into efficacy models, particularly large animal models where you can do serial blood levels of biomarkers or AUC for the drug, things like that. So, although we haven't in the past typically looked at efficacy models for safety information--we do our toxicology studies in otherwise health animals, efficacy models probably can be used for this, and I think there is at least some experience with that in looking at biologics.

Now I am going to mention the animal rule. The animal rule was passed, I believe, in 2001. I think that is when it was finally codified. This allows for use of animal studies to demonstrate efficacy for where clinical trials would be unethical and/or not feasible. It applies to new drug and biologic products. It is used to reduce

or prevent toxicity of chemical, biological, radiological or nuclear substances. Obviously, I think we can sort of see what the animal rule is really designed for, and that was for development of drugs to treat things like anthrax. Basically, we are talking about counter-terrorism measures. You know, antidotes for nerve toxins and things like that. That is what it is really designed for.

Drugs considered should have demonstrated safety in humans. That is one thing that is built into the animal rule. Now, whether or not that would apply to oncolytics, that is a different question and I think that is something for the panel to discuss. If possible, clinical activity in a relevant disease, although lack of clinical efficacy data shouldn't prejudice against consideration under the animal rule. We have had sponsors come in and propose to pursue a drug under the animal rule where there was no activity data in clinical trials in adults, let's say, as applied to what we are considering today. The important thing to consider is in what way can this principle be applied to pediatric oncology drugs. I think this is something that maybe would be worth discussing.

Juvenile animal studies can be useful for

safety determinations. They are not prohibitively challenging to conduct. You can dose rat pups from day seven on. In fact, people have even looked at beginning with birth, transferring drug in mother's milk and then starting to dose after weaning. There are all kinds of ways you can manipulate neonatal animal studies.

The available data doesn't indicate that juvenile animal studies need to be routinely conducted, but they might be needed under certain circumstances, as I have mentioned previously. But the database is limited and this conclusion could change. I don't think it will but, as with anything, as we start seeing more juvenile animal studies we will start looking back at these and deciding whether or not we made the right decision in our recommendation.

So, thanks and I appreciate your attention.

DR. SANTANA: Thank you. I am going to take the chair's prerogative and ask you two questions because I don't want you to leave the podium without addressing these. One is, can you give us an idea of the universe of where this is applied? I mean, how many times when there is a

new drug, either in development or a drug that is already out there, are we going back and doing either retrospectively, when is the drug is already out there or as part of the development plan, some of these studies addressing specific issues of toxicity? Is this a common thing that happens?

DR. HASTINGS: In juvenile animals?

DR. SANTANA: Yes, is this common or uncommon? That is the first question. Then a corollary to that is, are there specific animal models that address specific systems? So, is there an animal model that already looks at neurologic toxicity? Is there an animal model that already looks at cardiac? Or, is it really just this model and then we look the nervous system or we look for the heart system, and so on and so forth?

DR. HASTINGS: Well, the first question, yes, we have seen a number of juvenile animal studies. Dr. Karen Davis Bruno, who is the chair of that committee, has been keeping a running tabulation. Karen, do you know what the number is right now?

DR. BRUNO: [Not at microphone; inaudible]

DR. HASTINGS: Also, as I understand it from sponsors, when it was understood that we were

working on this guidance, if they were going to pursue pediatric development before they understood that we were looking at developing a for-cause guidance, in fact, a number of sponsors just did them. I mean, they basically just said we are going to anticipate that FDA is going to ask for them. So, yes, there are a number of them and some of them have been quite informative. I didn't really get into that because, frankly, I am not aware of a case in pediatric oncology.

As far as a preferred animal, well, no. I wish we could say that there is. You know, we have standard models in toxicology in drug development--rats, beagle dogs, cynomolgus monkeys and it is almost like those are the better models simply because we have just developed so much data with them that we understand what is going on there. If it is neurological though, you are probably wanting to think more in the line of a non-human primate like cynomolgus. But for, like, immune parameters probably rats would be a better model simply because we have the reagents to do that kind of study.

DR. SANTANA: Thank you for answering those two questions. I think they were relevant to

what you were trying to address in your presentation. I will invite Malcolm--he has the daunting task of being the last speaker.

Assessing Anti-Tumor Activity in Nonclinical Models of Childhood Cancer

DR. SMITH: I would like to thank Steve and colleagues at the FDA for sponsoring this meeting and for the invitation to speak here this afternoon.

I will be talking about NCI's initiatives to develop nonclinical models for pediatric oncology. Throughout the talk I will slip between nonclinical and preclinical. The slides are variably labeled that way but you will know what I mean. The three major things I will be focusing on are, one, why we need to be working in this area; two, why we are doing what we are doing; and, three, why we think it has at least some chance of providing useful information.

I have shown this slide at I think previous pediatric ODAC meetings, but it is the drug development pyramid and it makes the point that there are more agents entering Phase I studies in adults than we can move into children; then, more agents during Phase I in children than we can

conduct Phase II studies for; then only a very limited number of Phase III studies that we can conduct. We are not limited now at the Phase I setting. We actually could study more drugs in the Phase I setting. Where we really are limited is in moving to Phase II and doing all the Phase II and pilot studies that we need with these new agents, and then especially moving into Phase III studies and the one neuroblastoma Phase III study or rhabdomyosarcoma Phase III study that we may be able to do in the next three, four to five years.

To make a concrete example of this neuroblastoma and looking at the agents under evaluation now, these are all in pediatric Phase I or Phase II trials--a demethylating agent, decitabine, fenretinide, interleukin-12, the Trk tyrosine kinase inhibitor, oxaliplatin, HDAC inhibitors and then BSO. Those are the single agents or we could combine those with standard chemotherapy agents in different regimens. We can combine them with each other and try to inhibit some of the different pathways jointly that these agents inhibit. So, how are we going to pick which of these agents, which combinations to bring forward for the one neuroblastoma Phase III study

that we will be starting in two or three years? It is a daunting challenge to try to get data that informs that decision.

Hence, this is a primary need for some help with that from the preclinical or nonclinical area. If we had predictive nonclinical methods, it could contribute to prioritizing agents for evaluation against specific types of childhood cancer. To do this, we need a systematic approach opposed to what really has been a haphazard approach over the past twenty years. The systematic approach is required to assess the predictive value of pediatric nonclinical models.

In recognition of the need for such a systematic approach, the NCI board of scientific advisors approved committing ten million dollars to this effort over the next five years through the Pediatric Preclinical Testing Program. I will describe this in a bit more detail later but for now suffice it to say that this will be a systematic approach, primarily based on in vivo testing with xenograft models, but also having an in vitro component and making use of genetically engineered models when those are available and applicable.

So, the questions I am asked about this when I have talked about this are, well, why are you doing this? Don't you know that adults have used xenografts and xenografts don't work?--analogous to Pat Reynolds' question earlier. I would respond to this by pointing out three papers, and I will start with the last one, a review article that I would refer you to for marshaling of the arguments that xenografts can contribute to drug development and the take-home message there is better than commonly perceived but can be improved.

The first reference was a paper from the developmental therapeutics program at NCI, and the conclusion there was that although maybe a breast cancer xenograft didn't predict for activity in breast cancer, activity across a range of xenografts predicted that that was an agent that had a good chance of being successful when transferred to the clinic, not necessarily for the tumors that weren't in the xenograft models but for at least some cancers having activity.

The second paper, a more recent paper published last year in Clinical Cancer Research, made the point that using panels of xenografts for

a given tumor type increases the likelihood for correct prediction, and we will be focusing on panels of xenografts in our preclinical testing program.

This shows two figures from that paper. If you look at the one on your left, each of the squares represents a drug that was studied in the clinic. There is the Phase II activity, the response rate. And, it was studied in a panel of xenografts, and the readout there is the mean treatment to control. So, a low treatment to control indicates a high level of activity in the preclinical setting and high response rate in the Phase II, of course, indicates high activity there. So, you see the predictive value for at least two of these xenograft panels where activity in the preclinical setting in these ovarian xenograft panels and the non-small lung cancer xenograft panels predicted for Phase II activity for these agents.

The other point that I make when justifying why we think this has some reasonable chance of being successful is that we have the advantage of being able to make use of pharmacology to enhance a predictive ability of preclinical

models. We will be able to make comparisons between mouse pharmacology to human pharmacology and this can rule out the trivial explanation for activity in xenograft models. That trivial explanation for an agent being active in a xenograft model being that the mice tolerate much more of the agent than humans do. So, a human cancer implanted in the mice is going to be exposed to much higher levels than we will ever seen in the clinical setting and there is a good chance that activity will be seen but it won't be replicated in humans.

In the pediatric preclinical setting we can use both the activity of the agent in our pediatric preclinical models that test results, and also the comparison of the mouse PK of the agent with the PK of the agent in the initial adult trials. We will be studying these agents or we will be making our decision at a time after we have some initial adult experience.

So, the most promising agents then will be those that have activity in the pediatric models at serum levels that are actually achievable or systemic exposures that are achievable in humans. Peter Houghton gave examples of this and I will

just reiterate two of those. The topo-1 inhibitors, irinotecan where incorporating PK led to positive prediction for the activity of irinotecan against neuroblastoma. Then, incorporating PK correctly predicted inactivity for another agent that he described, sulofenur.

Peter mentioned the data that we have that support the potential for prediction, and I just list those, the data that he described for activity of agents in rhabdomyosarcoma xenografts mirroring the clinical activity of these agents, the correct prediction of activity for topo-1 agents against both rhabdomyosarcoma and neuroblastoma. Another point is that models now are not just limited to rhabdomyosarcoma and neuroblastoma. Peter described the Wilms tumor and some of the predictive supportive data there.

Importantly, we also have xenografts for acute lymphoblastic leukemia. Since this is the most common cancer in children and a major cause of mortality among children with cancer, it will be important to also look at this in an in vivo preclinical setting.

This is work from Richard Lock, published in Blood a couple of years ago, just showing the

blast cells in the patient and then growing in the NOD/SCID mice.

This is a table from that work showing that when these lines are transplanted into mice with no treatment there is a reasonably consistent growth pattern. With treatment with an agent known to be active against some childhood ALL cases there is substantial growth delay for some cases; moderate growth delay for other cases; and no growth delay for some. Importantly, this in vivo sensitivity to vincristine correlated with what we know is an important measure of sensitivity in ALL, the duration of the first complete remission. So, we have the capability now to look at these ALL xenografts to address this important disease.

An important contribution of the preclinical models now is in the area of molecularly targeted agents, and the ability to make preclinical pharmacokinetic and pharmacodynamic comparisons. Peter mentioned this and I will reiterate it. Especially important in this era of molecular targets, we can use these models to identify the degree of target modulation that is associated with anti-tumor activity, 50 percent inhibition, 75 percent, 90 percent, what is

needed in order to achieve anti-tumor activity; how long does target modulation need to occur to achieve the desired effect; and then particularly important for children, what are the serum levels or systemic exposures of the agent that are associated with the requisite levels of target modulation because it is going to be very difficult for most childhood solid tumors especially to be able to biopsy repeatedly tumor specimens to measure this in children so we can understand the pharmacology in children and target the systemic levels that we have shown in the preclinical models to achieve the desired level of target modulation. This is also an opportunity to correlate anti-tumor activity with gene expression profiles and protein expression profiles.

One area that we are working in to try to facilitate the evaluation of molecular targeted agents is a project called POPP-TAP, or the Pediatric Oncology Preclinical Protein and Tissue Array Project. This is a collaboration between NCI, both intramural and extramural, and Children's Oncology Group researchers. The objective of this collaboration is to develop tissue and cell arrays and protein lysate arrays of pediatric preclinical

cancer models, primarily focusing initially on xenografts and we are going to have close to 100 xenografts, different xenografts for which we will have these tissue arrays available for study by researchers. Also, Kahn's laboratory is determining the gene expression profiles for these pediatric preclinical cancer models, again focusing initially on almost 100 xenografts for this. Then, these data will be available for researchers as well. We hope that this project will facilitate the conduct and interpretation of preclinical testing of targeted agents in childhood cancer models.

The kind of complicating factors in testing molecularly targeted agents--the comment is sometimes made, well, you know the target is there, just go after the tumors that express the target. It is not that easy. One of the complicating factors is the promiscuity of agents. A targeted agent may hit multiple targets, some recognized; some not. The Bay compound is one of many examples. It was initially a raf kinase inhibitor. So, there is promiscuity of agents in terms of their targets.

There are multiple biological effects of

modulating a particular target of these so-called molecularly targeted agents so farnesyl transferase inhibitor in all the pathways that affects; the proteasome inhibitors in all the different pathways that that affects; Hsp90 inhibitors, all the pathways affected there. And, it is very hard, kind of on first principles of tumor biology, to predict a priori what the potential applicability of a particular agent such as this is to a particular childhood cancer based on just its biology. The preclinical testing then can allow identification of previously unrecognized or unsuspected activities that may have clinical relevance.

I am often asked, in terms of addressing preclinical activities, well, what about mouse genetic models? Why aren't you focusing solely on mouse genetic models? They have certainly made critical contributions to our understanding of cancer pathogenesis. In order to use genetic models for testing, not all models will be appropriate for testing. Really specific properties are needed, particularly short latency and high penetration for feasible testing are two characteristics needed and not all models have

that.

But there are some genetically engineered models for pediatric cancers that may have these characteristics and be suitable for drug testing. For example, the MYCN model for neuroblastoma may be appropriate and we will try to use that if we can.

The other caution is that a mouse is a mouse, and mouse biology is not the same as human biology. So, the lessons from the mouse genetic models may not apply directly to the human setting. There was an excellent review last year that really documented this issue and made the point that more humanized mice may more faithfully replicate human cancers.

The preclinical testing program that we have worked on over the last year or two to initiate will be based on panels of xenograft lines for the most common childhood cancers. It will incorporate an in vitro testing component along the lines that Peter Adamson outlined, particularly in areas like the combination studies which may provide valuable information.

We hope to be able to systematically test 10-15 agents per year, seeking to obtain agents

near the time that a commitment is made for the initial evaluation in adults so that, by the time the adult clinical experience is available and there is evidence that this may be an agent that could be studied in children, we will have preclinical data to better address the question of whether this is an agent that should be studied in children. This will be implemented via a contract mechanism with the primary contractor and the potential for subcontracts for testing specific cancer types.

The schema that Peter showed is shown here. I will just make the point here that we will be using panels of tumors. For example, if this is a rhabdomyosarcoma, each panel is represented by 6 to 8 to 10 different xenografts, and then testing at the MTD initially. When hits are identified, activity is identified, then being able to go and study the agent more intensively, look at a full dose response, obtain PK data if that is not already available, and do some of the molecular studies if those are warranted.

A critical issue is addressing the intellectual property issues. We have made efforts over the past years to develop, in collaboration

with academic investigators and pharmaceutical sponsors, a model MTA. This model MTA will be used for all transfers by companies of their proprietary compounds to NCI-supported investigators for preclinical testing. Acceptance of the model MTA, and it was included in the RFP for establishing the preclinical testing program, but acceptance of the model MTA is a requirement for participation in the program.

I actually have some copies of the model MTAs. There is one for transfer of the agent to MCI and there is one for transfer of the agent from MCI to the test sites. But Dr. Sherry Ansher is the CTEP contact for those. If anyone wanted copies, I would be glad to provide those to you.

In summary and in closing, appropriate prioritization is key to future treatment advances for childhood cancer. If we make good decisions in terms of which agents we bring forward, and particularly to the Phase III setting, we have a chance for making advances. if we don't, then our advances will be limited.

The Pediatric Preclinical Testing Program may contribute to successful prioritization but systematic preclinical testing of all agents

entering clinical evaluation in children should become the standard of care, not because we know what to do with these data now--we may have ideas of what to do with these data, but because a systematic approach is what we need to allow validation of the panels and to optimize the pediatric preclinical tumor panels. Thank you and, again, thanks to the FDA for this opportunity.

Committee Discussion

DR. SANTANA: Thank you, Malcolm. We have a few minutes for questions for presenters before we go into the period of answering the questions. Dr. Przepiorka?

DR. PRZEPIORKA: Thanks. Two questions, one for either Malcolm or Peter. Peter had a slide up there of I think it was MMI114 looking at a single dose or dose schedule against a series of tumors. If I recall, your conclusion was it was not a very active drug because the AUC was ten times greater than what one could expect to achieve in humans. I was somewhat disappointed because I could think of three or four drugs that we already use for which we could probably have made the same conclusion based on a single dose schedule being tested.

So, my question for either of you is, especially with the development of the new program, is there an established panel of dose schedules that will be used for drug testing so that you know when a single high dose is going to be effective as opposed to low continuous exposure before a drug is thrown out?

DR. HOUGHTON: I think in the case of NGI114 we have basically done other schedules. I think what we would hope is that a fair amount of optimization will have been done if we get a drug from industry that is going into a clinical trial, that a lot of the various schedules that have been examined and information on which are the best schedules will be made available at that point. I think if you look at the size of the screening program, if we went to doing the classic schedules that you are going to use in the clinic, I don't think the screening program has the capacity for those; it certainly doesn't have the funding to do that. So, I think for most drugs that will come from industry, they may well have that information already so that would at least allow us to do the first cut using the optimal schedule that they have and, in most cases, those have been quite accurate.

DR. PRZEPIORKA: If one has knowledge of the mechanism of action and the pharmacokinetics, could one potentially come up with the three best guesses and so not have to do a whole bunch of different dose schedules, or is that not a reasonable approach?

DR. HOUGHTON: Again, a lot of that information will be available to guide how we test the drug in the screening program. I think we still have to go to the MTD. I think that is probably appropriate because one of the things you want to do is get some idea of the tumor sensitivity relative to an MTD in the mouse so ultimately you want to do that with respect to pharmacokinetics. So, irrespective of whether you know the mechanism of the action of the drug, I think the consensus was that you go for the MTD even if you have a molecularly targeted drug where you think it is a specific kinase inhibitor. That is for two reasons. One is if you see no activity that probably tells you that, you know, this is not a drug that is suitable for treating certain pediatric cancers. The other is that despite having very strong evidence that a specific target is, indeed, the target, when you go to the MTD you

may, in fact, reveal additional activities. I think what we are trying to do is the minimum amount of work, not because we don't like to do any work but the minimum amount of work means minimum utilization of resources to do a first cut to identify those drugs that are worth pursuing, and maybe looking at scheduling issues but to eliminate those where we feel there is very little reason to pursue that.

DR. PRZEPIORKA: If Dr. Chand Khanna is still here, I have a question. I mean, GLP came around because of some major issues in drug development for adults and I would hate to see the same problems arise in pediatrics because GLP was not applied. The comment was made earlier that it is too expensive for a vivarian in academia to actually run under GLP but, given all the rules that govern how you deal with animal care nowadays, I can't imagine that it is not already running under GLP. Does the Center for Comparative Oncology animal housing at NCI--in your experience, is that run under GLP and is it really a stretch to try to get everybody who is going to be doing preclinical testing to do that?

DR. SANTANA: Can you come to the

microphone, please?

DR. HIRSCHFELD: While he is coming, I want to request the permission of the chair to have Dr. Khanna and Dr. Meltzer take some empty seats at the table and to have them join in the discussion. I think there are empty seats between Dr. Weiner and Ms. Haylock and there is an empty seat next to Ms. Ettinger.

DR. KHANNA: Yes, a point of clarification, at NCI we actually aren't going to be managing pet animals in trials. We will be managing those trials through veterinary teaching hospitals that do operate under GCP guidelines in many situations. So, that GCP hurdle is certainly passed at many of those sites that we will be working with and, in fact, it will be a requirement for them to be involved in our cooperative groups.

DR. SANTANA: Donna, not to take this discussion down a different route, but those for us who are not familiar with the issues related to GLP, since you hinted that there was an issue, could somebody summarize what those are?

DR. HIRSCHFELD: I think we have a lot of experts in the room but, in brief, the International Conference on Harmonization, as well

as the FDA, have adopted standards under which animal studies are conducted. These standards collectively are referred to as Good Laboratory Practice. Is Dr. Hastings still here? Do you want to add anything to that?

DR. HASTINGS: [Not at microphone; inaudible]

DR. SANTANA: Please us the microphone because we really need to listen to the discussion and sometimes it is difficult, and also record it for the record. You can take the podium; that would be fine.

FDA PARTICIPANT: GLP has many components to it. It includes the test article and how stable it is. The composition has to do with the people that are involved with the research, like their CV being on line, how they have been trained. It has to do with the instrumentation and how they are calibrated or if they are appropriate for the testing that is being done. It has to do with the animal husbandry, and how they are kept, the room and the building, and many other components to it.

DR. SANTANA: Donna, did you want to elaborate on that?

DR. PRZEPIORKA: Yes, I think from all the

talks that I have sat through, all the way back to orientation, I believe GLP came around as a result of some issues regarding fraud and poor science in the late '60s, early '70s. I was just looking to see if the poster was still up because I think I remember the poster being up during orientation. So, GLP came around as a result of a lot of problems with scientific integrity in the initial preclinical work that was handed in with drug trials supporting FDA approval, and to have that happen in the pediatric setting right now would probably be a huge step backwards for pediatric drug development.

DR. ADAMSON: I just want to clarify that there is a difference between GLP and GCP. Without question, pediatric trials are according to GCP. What you are saying is the animal clinical trials are going to be conducted according to GCP. That is a different level of work but that is the standard in pediatric drug development trials.

GLP, as we have just heard--there are very few academic laboratories, adult or pediatric, that do work according to GLP. That is the reality of academic laboratories. There are very few that do it according to GLP because the costs become

prohibitive. There are some laboratories that can do it but I think they are a distinct minority. Without question, would every place like to do it according to GLP? Yes, but the funding is simply not there to meet those costs.

DR. WILLIAMS: I must say that working with our pharm tox colleagues we do not demand GLP when we see a new IND, but we do demand that they analyze where it differs from GLP and justify those differences.

DR. SANTANA: Malcolm, were you going to make an additional comment?

DR. SMITH: In the RFP for the preclinical contract we did not specify GLP. That was at the recommendation of colleagues in the Developmental Therapeutics Program. You know, basically it is what Peter was saying, that it would limit the pool of researchers who could do that work. We will have appropriate procedures in place so the credibility of the results will, we hope, be above question but we have not required that they meet the GLP requirements in the RFP.

DR. SANTANA: Dr. Hirschfeld?

DR. HIRSCHFELD: I will make one further comment and then maybe we can go to the questions.

GLP I think is more precise than GCP. GCP is very open to interpretation and that was one of the rationales for having our discussion this morning, and it is a continuing source of guidances and directives and other documents attempting to decide how GCP can be applied to any particular study, whereas GLP tends to be more explicit.

DR. SANTANA: Good. Any other questions to the panel members or discussants?

DR. REYNOLDS: I wanted to tie a little bit of what Eric was saying this morning to comments made by Peter and particularly by Malcolm where you suggested a standard of care would be preclinical testing if we are engaging in human studies in pediatrics. I think it would seem that given what Eric was saying--this was really not a point of discussion in the morning when we were talking about monitoring but he did point out the sort of ethics dilemma involved in facing a Phase I study where you are looking at having to deliver some prospect of benefit to a patient in the context of doing the study. I think I would like to suggest that we incorporate or think about some sort of way that the agency might incorporate Malcolm's suggestion of a standard of care, of

having some sort of preclinical data in the pediatric tumor setting before engaging in testing these agents in the pediatric setting.

DR. SANTANA: Peter?

DR. ADAMSON: I would actually put out a caveat that that would be a goal to try to realize perhaps within the next five or ten years. The large majority of agents today that are active drugs for children with cancer have not gone through preclinical testing. There is a lot of inactivity in industry with very important drugs. So, it is an ideal we would like to move towards but I think we are many steps away before saying that that is the standard of care.

DR. SANTANA: Dr. Smith?

DR. SMITH: The other caveat would be that in the future it could be a standard of care because we have predictive models that we are confident of and it makes sense to act on our knowledge of these predictive models. That is in the future, why it should be the standard of care. Why it should be the standard of care now is because if we don't do it systematically and obtain the experience, then we won't ever get to that future. So, for now the standard of care is

because only by systematically approaching this problem can we develop the data that gets us to the point where we are confident making decisions based on these data.

DR. REYNOLDS: Absolutely, but I think what Peter said in one of his slides is quite true, and that is under the ideal circumstances of a good laboratory model, if you can't get good responses in your disease type you are probably unlikely, almost assuredly unlikely to get those responses in the children. So, I think that doing some testing to exclude agents that we then would not be exposing children to when they have no prospect of benefit based upon what is probably a predictive model--that is, if you don't get any activity in the lab you are probably not going to get it in the clinic--should be at least a consideration.

DR. SANTANA: Dr. Houghton, I think you had a comment?

DR. HOUGHTON: Only to add that I think in five years time we will have a much better idea of whether this is correct or not. I think the one thing that perhaps didn't come out strongly enough from maybe the three of us is that what we are proposing in terms of PPTP is an experiment and we

don't know how accurate the models are going to be. We don't know what the flaws or the limitations are.

So, in a way, I think it would be also inappropriate if you had no activity in the model not to pursue that at a clinical level because, in fact, they may be very important experiments that will reveal the fact that the models have limitations. What we want to know at the end of the day is with we are on the right track or the wrong track, and if there are limitations to try and address those in the next generation of models.

One of the biggest problems I see in the development of models in preclinical development, in the thirty years I have been playing this game, is that we have these transitions, we transitioned from syngeneic rodent models to xenografts, to in vitro systems to xenografts, to perhaps transgenics and nobody has taken the time to look back to see what the problems were of the previous model that would then allow us to develop a better model. So, the next five years may be very revealing in terms of the current models we have and their limitations but give us the information that the next generation of models won't make the same mistakes

as the previous models.

Questions for Discussion

DR. SANTANA: With those words of wisdom and advice to all of us, let's go ahead and try to tackle the questions for discussion. FDA is requesting that we comment on three issues and, for the record, I will go ahead and read the introduction and the questions.

Because of the limited number of pediatric oncology patients and because of the problems unique to pediatric drug development, it may not always be feasible to evaluate all aspects of efficacy and safety in clinical studies. In some settings, extrapolation of results from nonclinical studies may be appropriate.

The first question is what types of questions that are of potential clinical relevance but are not feasible or acceptable to answer in a clinical study could be addressed by nonclinical studies? Then various examples are given after the question that potentially could fit the answer that we are being asked to provide.

I want to comment that one of the things that I gathered from some of the discussion and presentation this afternoon is that some of the

field is moving to molecularly targeted therapies, whatever that means, and we may have limitations in our patients in being able to correctly or early on assess the correct target or do multiple biopsy samples, etc., to see whether relevant targets are being affected. I think in that setting, in which the ethical issue of providing multiple biopsies in a patient may be relevant or may not make the clinical studies feasible, these models could be used to address those very early on so that when we get to the stage of testing these drugs in patients, then sampling strategy may be very limited or may be focused to such a degree that ethically it doesn't become a constraint for the study. So, that is one setting where I think some of these preclinical models potentially could help us in terms of limiting the ethical barriers we may have when we introduce these molecularly targeted drugs to our trials. That is one example that I think would be relevant. Dr. Reynolds?

DR. REYNOLDS: I would like to suggest another example. If one is dealing with agents, two new molecular entities or new agents of which one may have some modest activity and the other, as a single agent, may have very little activity but

in combination in preclinical studies have striking synergy, requiring that you demonstrate activity for each individual agent in a patient, whereas if you went in with the combination you might get striking activity, and using the preclinical data or nonclinical data, however you want to describe it, to justify the approval of the agent as a combination I think would make some sense, and would spare children the ethical dilemma of being treated potentially with an agent that is predicted by preclinical data to be fairly non-effective, yet might contribute to the overall response of the two agents in combination.

DR. SANTANA: Dr. Adamson?

DR. ADAMSON: In looking at the examples, Steve, that you have here, almost all of them are looking at host and not tumor. I think that is fine and helps us think about what you are after. What I would caution is that we don't know, even as far as host response or, you know, developing animal models, how predictive they really are, and the experience with the fluoroquinolones I think is a good one. We are using them and we are still learning what the real risk is. We should not delay the initiation of pediatric testing of

anti-cancer agents for the results of these types of studies because in the balance, of course, are diseases that carry a far more certain outcome for certain subpopulations of patients.

So, yes, we need to embark on some of these. We need to realize the limitations as far as predictiveness, and we should not mandate that they become requirements to being the human testing of anti-cancer agents.

DR. SANTANA: Susan?

DR. WEINER: One of the things that occurred to me was that at least some nonclinical data could be very relevant, obviously, to patient selection for trials.

DR. SANTANA: Other comments or issues related to this question? What I heard, Steve and the rest of the FDA, was that these examples you gave are relevant and, obviously, they are dependent on what you are really after so you can't put them all in one box for each drug. I think you have to consider them based on each individual agent which is more important in terms of what you want in terms of using preclinical data.

You heard my comment about molecularly targeted therapies and potentially how that could

be an area where some of these models could be used.

You heard a little bit also that some agents which potentially may not be totally active but in combination, if you could do that preclinically, you could demonstrate some additional activity before you actually take it to patients.

Then I heard comments related to potentially how this could be used to identify potential populations if you could do the preclinical work in animals, looking at some markers that potentially could select the populations that would most benefit once you decide to do the trials.

Then the last comment I think came from Peter Adamson that while we do all this, this should not hinder our ability to get the initial clinical pediatric trials started but that they should occur either in parallel or maybe a little bit earlier, or wherever in time, but certainly not to hinder the development even if this data does not exist because, actually, a lot of the questions may come after you do the initial Phase I, some early Phase II studies, and you want to go back to

certain models and ask the questions that may be relevant by scheduling--are you hitting the right systemic exposure, and things like that. I think the beauty of this system is that it has to feed back to what you knew from before. Hopefully, that is something that we will get from this experiment that will be ongoing in the next few years, that information will be used to go back and then ask the relevant questions about why it didn't work so that then, for the next series of experiments, we can potentially address that. Dr. Helman?

DR. HELMAN: Victor, I want to reiterate I absolutely support what you say, but also just to reiterate what I think both Malcolm and Peter Houghton said which is that, you know, in point of fact this is an experiment. Many of us have spent our lifetime trying to find better ways to identify screening ways to pick winners for kids and for treating our patients but we don't know.

Just as an example and, again, to support what you said and what Peter Adamson said about not mandating or requiring that, I think the GI stromal tumors is a very good case in point. All we knew is that GI stromal tumors were defined by their mutation in the C KiT receptor. That was how the

entity was defined by a group of investigators in Japan, and it allowed us to separate them from what was called up until then GI leiomyosarcomas. All we knew was that a drug that was active in CML had in vitro activity against C KiT and that was the extent of all the modeling of the data, period, before it was given to a patient with a GI stromal tumor. The rest is history. There was no preclinical data. There were simply two observations, GI stromal tumors had mutations in C KiT and the STI571 AK gleevec had activity in vitro against inhibiting that kinase. Everything else came later. So, you know, we were lucky and I will take luck over anything else any day. So, I think, you know, maybe we will be lucky again.

In retrospect, you know, Paul had this data to say that by profiling he could predict, and I would like to hope that in preclinical models we could say that it was absolutely clear that this would have been a winner but we don't know that yet.

DR. SANTANA: Paul?

DR. MELTZER: I just want to make one comment somewhat in the same vein. I think in pediatric oncology it is extremely important to

always bear in mind the very large spectrum and number of rare cancers that we encounter and I would not like to see those diseases orphaned from the hope of developing good treatment because we mandate the need for a preclinical model which will never be practical to develop.

DR. SANTANA: Very good point. I think the practicality of the issues that we have to deal with in tumor systems in pediatric oncology is very relevant to the discussion.

DR. DAGHER: Steven can also address this. I don't think the intent of the question was to imply examples where there would be additional mandates. I think it was actually in response to issues that have been raised by the cooperative groups themselves and the Phase I Consortium about those kinds of hurdles. It probably wasn't the intent to ask for additional mandates, although often when FDA asks a question, that is usually what the fear is, that we are thinking about additional mandates. That wasn't the intent.

DR. HIRSCHFELD: Just to add to Dr. Dagher's precisely right answer, the intent was how can we better inform the data we have? So, that was the rationale for the entire discussion this

afternoon, how can we use nonclinical data so that we can improve our conclusions and improve our designs and use our resources most effectively?

DR. SANTANA: Good. Let's move on to question number two, and I think I am going to ask the FDA to clarify this question a little bit for me, but the question relates to what types of evidence and data would be recommended in each of the following domains to allow extrapolation from nonclinical data and be informative for a clinical condition. There is pharmacology and pharmacokinetics; safety; efficacy; behavior; long-term effects; developmental aspects; and then, question mark, other domains.

Maybe I would like the agency to clarify for me what do they mean by types of data or types of evidence so that we can address this appropriately?

DR. HIRSCHFELD: This is a rather theoretical question but it should be grounded in the limitations of models and should be grounded in data, but there are circumstances where one has information in a domain and would like it to be predictive, or at least informative, for some other domain. So, in some cases formal rules or formal

mechanisms have been identified. As an example, for the conversion from a laboratory measurement from a biomarker to what could be called a surrogate, where the surrogate is for clinical benefit, the NCI and others have made specific recommendations on what type of evidence one would like to see. Going back about 160 years, there were initially observations which were formulated by Profs. Koch and Henley that there are some conditions that would be met between the identification of a microorganism and its causative role in a disease.

So, we don't expect that for all the various domains of clinical interest there are formal rules to be identified, but what we would like to have is some commentary on the type of evidence and the strength of evidence so that if someone is proposing a nonclinical approach we could get some advice on whether we would consider the data that are being offered as valid data, as informative data. If you want further elaboration we could try, but I think that is the general concept.

DR. SANTANA: If I understood you correctly, I am going to try and see if I follow

you to contribute to (a). I think we heard this afternoon how systemic exposures or AUCs of certain drugs can potentially, in certain animal models, predict reduction in tumor volume--not cures but reduction in tumor volumes at the appropriate MTD that are clinically relevant. So, I think that would be a good example that, if there was good systemic exposure data at the MTD that was clinically relevant in adults that then was going to potentially begin the pediatric studies at that MTD or near that MTD, and there was good response data in animals at that MTD, to me, that would be information that would be relevant to addressing the issue of how pharmacokinetic data could be used in a nonclinical setting in a preclinical kind of model.

DR. HIRSCHFELD: So, if I may paraphrase, and have that then inform the answers to the others, and they may not be the same types of answers, but one has a set of techniques that are available in the nonclinical model that are also available in the clinical model so that one can make direct correlations because the technique for determining AUC is the same in the nonclinical model as in the clinical model and then you are

relating the readout, applying that technique and then making a direct correlation. That would be paraphrasing it, but the concept there is that you have techniques which are identical or potentially could map onto each other, and having that assay availability is what lets you make the extrapolation.

DR. SANTANA: Peter and then Donna.

DR. ADAMSON: I think other examples, and it comes back to the need to do tumor biopsies or repetitive tumor biopsies--I think if you can demonstrate in an animal model or, preferentially in animal models, that you have a surrogate that is reasonably predictive of what is happening in the tumor, that should weigh in when looking at the effect in a patient. So, if you are down-regulating expression of a target in a tumor but you also see it in a lymphocyte and you have a pretty strong correlation in your animal model, it is a lot easier to get lymphocytes from children than it is to get tumors from children. So, I think that should weigh in as part of proof of principle that you are hitting a target when you actually don't have repeat access to that target.

DR. SANTANA: Donna?

DR. PRZEPIORKA: Actually, I would like to ask for additional clarification on this question because I recall one of your first slides in your prior talk was, I believe, that the rule is that you need at least one clinical trial as supportive evidence. My question is regarding strength of evidence. Do you want us to be considering sufficient strength of evidence to be the sole supporting data for that one clinical trial because pediatric cancer is an orphan disease and you may not get the chance to do anymore clinical studies?

DR. HIRSCHFELD: Well, if I understood, and we can try to clarify this to be sure we are both addressing the same issue, yes, it is most likely that many pediatric malignancies, for reasons that Dr. Meltzer mentioned, because they are quite rare, will only have one study being done. Dr. Smith elaborated just on the resources of that too. So, if we are only going to get one study, there are ways that we can improve our interpretive ability of whatever the clinical outcome may be, either safety or efficacy or long-term effects or something, by using nonclinical data.

DR. SANTANA: Malcolm?

DR. SMITH: If there is the one pediatric trial, the one Phase III trial that shows a p value that is favorable and you are looking for something else to help you justify that this is approvable, then looking at a robust preclinical data set that shows the same kind of responses or anti-tumor activity in the preclinical models would seem to be supportive at least and provide you some additional confidence that the agent was going to behave in larger groups of patients as it had in the trial.

DR. HIRSCHFELD: Let me turn it around a little bit. I guess initially all of you sitting on that side of the room--and since this is an audio recording, it would be Drs. Smith, Helman, Adamson and Anderson--you are starting a fairly extensive program which you acknowledge is an experiment. So, one way of helping us would be how are you going to know at the end of five years that you have had a successful or an unsuccessful experiment? And, what are you measuring that is going to determine that? We would be interested in getting an answer from each of you.

DR. SMITH: I will say something and then let Peter chime in as well. You know, some of the testing that we do will be to go back and take

agents that are already being used, for which there is some background response data from the clinical setting, and look at the operating characteristics of the various tumor panels against those agents. So, there will be kind of building of a baseline for agents that we already have activity data for. The others will then be looking ahead prospectively. If we have agents that have been tested and moved from the preclinical to the clinical setting, is the activity observed preclinically replicated in the clinical setting?

DR. ADAMSON: The clinical endpoints are going to be Phase II endpoints for this experiment, and you have probably heard the reasons why from Malcolm's talk as far as our ability to do Phase IIIs. But some of those Phase II endpoints are going to be traditional objective response rates or time to progression and I think in part may depend on the agent and our ability to monitor those endpoints.

But I should point out also that even in the ideal setting in the next five years where every drug that we potentially want to study will be put through this system, this is not going to be the only path to doing a clinical trial in children

with cancer. I can think of a number of circumstances where almost independent of what we see in our model system we are going to be doing clinical studies. The obvious examples are agents that have remarkable activity in adult cancers. We are going to look at them in pediatric cancers like we have historically looked in pediatric cancers.

And, part of the experiment will be if, in fact, the model predicts lack of activity and we go ahead because of other justifications and find the lack of activity, that is going to also help the negative predictive side of things. The positive predictive side of things, whether we look at relative response rates of simple yes/no, it met activity thresholds or not, I think will depend upon how many patients and how quickly we can get Phase II trials going. But there will always be more than one path to get a trial into children with cancer. The goal, however, will be to put everything that, for whatever reason, has got to a clinical trial through our model system so we can learn both positive and negative predictive values using Phase II as the endpoint. We would like one day then to start building in toxicity information but right now that is a primary goal of this

program.

DR. SANTANA: So, if I understood, I think you guys are going to try to address (a) and (c), the pharmacology and pharmacokinetics and efficacy in your models and use that data to decide whether you move on to different model systems or whether you start to introduce other domains, like looking at toxicity and things like that.

DR. HIRSCHFELD: Were there other comments?

DR. HELMAN: Well, again, I maybe would rather address not necessarily the predictive value of the models but the biologic importance of gaining more information. For example, you know, you heard Malcolm briefly discuss the hope that we can have both some protein profiles, RNA profiles, and if there are subsets--I mean, we are going to use six to ten models so it may be--I have yet to do even a mouse experiment where I consistently cure 100 percent of the mice. Usually it is 90 percent in really good experiments, and sometimes 60 percent. So, if we can identify correlates of response, things that Paul Meltzer talked about, and then find that these are, in fact, important biologic discriminators between people likely to

respond, for reasons we may have no idea, and just generate hypotheses and if that correlates at all with somehow what we then can use in the clinical study, I think we will make some important steps forward.

I would just make the comment that it is something we try to hold ourselves to now because, you know, I think although we all like to think that there are ten more gleevecs out there, the likelihood of hitting a grand slam when we do clinical studies is extraordinarily small. So, if we do a clinical study with a therapeutic endpoint and the therapeutic endpoint is negative but we learn an important biologic principle, we will continue to make progress. If the only thing we learn is that this is inactive, we have put a lot of patients into a study that we come out not knowing anything more, other than that this thing is not active.

DR. HIRSCHFELD: Right. If I may just follow that up, that is exactly the direction where we would like to get some more advice on and thinking. So, could you elaborate on what you would mean by an important biologic observation even if the clinical result is disappointing?

DR. HELMAN: Well, the easiest thing would be we have a kinase that we think is important for the biology of the tumor. We give a drug. It inhibits the kinase and all the patients progress. In the end we have learned a very important point which is that that enzyme is irrelevant for the progression of this disease in a patient. I think that is an incredibly important observation to make.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: I think that one of the things we have to keep in mind when we are talking about these kinds of transitions that you are talking about, Lee and Peter as well, is that the clinical experience in your Phase IIs will be pretty much in patients that are refractory to existing agents. In some diseases one can imagine that is sort of like up-front patients but for the most part that is patients who have gone through therapy and maybe years out from therapy and it recurred.

So, I think in the context of that and thinking about the way the FDA looks at things where they generally approve an agent for a specific indication, like for second-line therapy

in disease X, we have to keep that in context in the preclinical modeling and we have to make sure that the preclinical modeling doesn't just reflect up-front patients but that it also reflects this refractory population so that we can make those correlations. For example, what you were talking about, Lee, where you hit your molecular target and you get zero responses, that doesn't mean that the agent wouldn't necessarily work in up-front patients and be an effective agent, and maybe your preclinical models would have said that it worked but then they all developed drug resistance that got around it.

So, all those are very complex issues and I think we are going to have to spend a lot of time thinking about these but, more particularly, spend time developing the models so that they reflect the clinical setting as much as we can.

DR. SANTANA: Steve, did you get what you wanted from the panel?

DR. HIRSCHFELD: If I may summarize at least what I heard, and then I will let you, of course, do the more formal summary as we pursue it just a little more because I think this is an important discussion, the context would be that

people are very interested in nonclinical models. The question is how informative are those data. So, what we have heard so far is that if you have the same technique to measure something, whatever that may be, in the nonclinical model and the clinical model you can do a direct correlation.

If you have surrogates in the clinical model that could map onto the nonclinical model, without defining how those surrogates are validated but we will presume that there is a validation process in effect, that could also be used as a mechanism to inform.

We also have an approach, to go back to something Dr. Meltzer referred to, training, that we have historical clinical data which then can be used to validate a nonclinical model by using the same types of agents in the nonclinical model and seeing if it correlates to the historical record. So, that is yet another approach.

Then we have prospective testing as an approach where we would ask a question of the nonclinical model and ask either the same or what we think is a related question to the clinical model and see if the answer comes out in a way that it is either identical or can be mapped.

Then, lastly, we have biologic correlates where we are not asking a specific outcome mechanism of the clinical circumstance but we are just trying to pick up information to help mechanistically understand, and then go back to the nonclinical model and use that as some form of evidence.

So, that is what we have heard so far, and I think that is all highly useful but, since this is a new area, we want to take the opportunity while we have the expertise available and these presentations fresh in mind to see if there are other aspects that ought to be probed because in some ways we can, hopefully, at least inform if not partially drive a research agenda to improve the validation process.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS? Steve, in general what we have been thinking about in terms of when you think about labeling indications and looking for a positive result is to say, okay, this has efficacy in a particular tumor type. What about the negative condition? For example, if an agent was to go through clinical trials and show activity and have a registered indication for a pediatric tumor

but preclinical studies showed that there was a subset of that very disease that was very unlikely to respond to it and there were some limited clinical correlations that showed that was the case, could that be incorporated in the label and used as informative information for pediatric oncologists? How would the negative side be approached?

DR. HIRSCHFELD: Well, that is exactly one of the scenarios we have been anticipating. I will give a very brief comment on the aspects of that. First, the question is not restricted just to product labeling. We are in a position of attempting to advise people on a continuing basis, primarily the pharmaceutical industry but also investigators, saying what type of studies would you like to see? This is a question that is asked essentially on a daily basis, and all of us spend probably at least 40 percent of our time meeting with people and attempting to answer their questions in this regard. So, I would view it as the spectrum, and that includes our colleagues whose focus is the domain of nonclinical data. So, I would view this as a spectrum of how to best utilize resources all throughout the developmental

cycle of any product and not restrict it just to the labeling.

Now, the other aspect is how can we use negative information? We have used that clinically but I think what you are asking, and this is something that we discussed in April, 2001 previously, and that is should negative data inform us to not invest the resources nor expose patients to risk for a given agent? Now, three years later almost, we would like to ask the question--we are very interested in that because of the potential savings, but what kind of evidence should we use to have confidence in those negative data?

DR. REYNOLDS: If I could just ask Peter, your point being, well, if the agent has some activity some place it should be tested in pediatrics, where could the interface between preclinical model testing that shows it is probably not going to work and limited clinical data in the pediatric setting come together to diminish the number of patients exposed to a potentially ineffective agent?

DR. ADAMSON: As Peter Houghton said, I think until we do this systematically we are not going to be able to answer this question because we

are just going to have biased data. So, if we can do it systematically and we can build an experience as far as what these models' positive and negative predictive values are, then I think we really can start making informed decisions when we see negative data that we shouldn't pursue it.

Given the limitation of resources, even before we have that data we are likely to apply some of this on an assumption that they are going to be predictive. But historically, as well as in the current environment, when an agent comes on market for an adult indication it will almost invariably be used by physicians of children who have refractory cancer. That is the reality. So, we might as well, for agents that are clearly active and as long as it is not beyond the realm of scientific plausibility--I mean, we are not studying estrogen receptor--well, I shouldn't say that; probably people are--

[Laughter]

--someone should be able to come up with an example of what wouldn't be used in a child. These drugs are going to be used until we have convincing evidence our models have both positive and negative predictive values. As Peter said,

hopefully, in five years we will be able to give you a better answer to that question.

DR. HIRSCHFELD: True enough. I will just state that we have labeled products that do not have what we consider to be activity in children on the basis of clinical data, sometimes using up to 100 children with no evidence of efficacy, at least in a particular disease or particular dose. We have labeled these things, that they should not be used in children and we are very interested in making sure that there is not inappropriate exposure.

DR. SANTANA: Kind of following that discussion, I think the issue of negative data--you know, it depends on whether you can explain why the data is negative. That is the critical issue. It is not that it is negative data because negative data can be very good data. It is can you explain why it is negative, why it failed? If you can find the reasons why in your particular experiment it didn't work, to me, that is very informative data and it should not go out with the baby. You know what I am saying?

So, it is a very theoretical discussion of this issue because if you don't do the experiment

correctly you wind up with negative data, but if you do the experiment correctly and you wind up with negative data and explain why it was negative, to me, that is an advance and I think that should not be thrown out. Donna?

DR. PRZEPIORKA: Actually, just thinking about Eric's slides from this morning indicating that in the pediatric setting at least we are looking more towards beneficence and doing good for the patient, and having sat on an IRB, I was jut wondering under what circumstances would I get a protocol for a pediatric study that says there is no evidence that this drug is effective in tumors that kids have but we are going to do a Phase II study? That would be a very difficult protocol to pass through an IRB.

DR. ADAMSON: I agree but there are a lot of protocols that come where there is no data in children. It is a cytotoxic and there is no data in pediatric models and we do those studies because we accept that cytotoxic agents likely do have activity in pediatric malignancies as a class. It is a horrendous problem when you think about how little data we base it on. There has to be some scientific plausibility that the drug is going to

work.

Related to that, I can almost guarantee that gleevec has been tried in every pediatric malignancy to some extent. What we would much rather do is say let's study it where we think there is scientific plausibility, and we are doing that now on very limited data, basically which tumors do we think express kinases that gleevec might inhibit? At least that gives us scientific rationale and will give an answer. If it is negative, I think that is important information because then at least we have the data, we put it out there and people aren't exposing children to gleevec simply because it is the most active agent in CML. The same is true for adult malignancies as well. I bet gleevec has been used in virtually every adult cancer that exists by someone.

DR. KHANNA: It is also used in almost every veterinary cancer--

[Laughter]

-- but one thought I wanted to follow-up with on Peter's comments was that the models are validated or found to be predictive within the context of the agent that was assessed so that agent X with model Y, if there is activity, doesn't

say that that model is a predictive model for a cancer in general. So, I think there is a complexity there that has to be incorporated in the next step of the analysis.

DR. SANTANA: Dr. Grillo?

DR GRILLO-LOPEZ: If I may, I would like to focus on the issues at hand in a little bit different way. Clearly, the medical need that we are discussing is a need to make new effective therapeutic agents available to children as soon as possible. Now, in the setting of the interaction between the agency and a pharmaceutical company you might look at two extremes. One extreme might be where an agent is to be developed exclusively for a pediatric malignancy and may not have any applicability in adult malignancy, and those may be very few and far between. But in that situation I guess the agency has to be more rigorous about the clinical data that needs to be submitted and supported by preclinical data than the other extreme, an agent that is clearly active in adult malignancies and where you could make the extrapolation that it should be active in pediatric malignancies.

Most of those agents are the agents that

we have today in our armamentarium, and most of them have been approved with very little pediatric experience, if any in some cases. One of the questions is if you do have an agent that is very active and that deserves to be approved for an adult malignancy whose responsibility is it to do the studies to show whether or not it applies in childhood malignancy? On the one hand, there is the need to find out; on the other hand, there are all of the obstacles that we have discussed today and the fact that there are not enough patients of pediatric age to go around. We can't do the studies in all of the available agents even today and on the other hand there is the need that we have. So, as a medical community interested in the cancer patient, we need to find out whose responsibility it is to do those studies.

DR. SANTANA: I think it is all of our responsibility, everybody in this room.

DR. GRILLO-LOPEZ: I think that is the answer.

DR. SANTANA: That is why we are here and we have been here for a long time.

DR. GRILLO-LOPEZ: Let me go further, that answer says that it is not the exclusive

responsibility of a pharmaceutical company and, therefore, should not be a requirement for approval of an agent that is shown to be active in adult malignancy. However, how do we approach the issue?

The issue can be approached in a variety of ways with the support of the nonclinical data that we have discussed here today, and the simplest way might be to produce clinical and nonclinical evidence that the pharmacology and the pharmacokinetics are similar to those of adults and that the safety profile is similar. That could go into a package insert without requiring that it be an indication. Another more stringent way would be to have it go into the package insert of an indication, and there you would require at least Phase II trials as a minimum.

DR. HIRSCHFELD: Rather than addressing the specifics of what goes in product labels and what does not, I would like to summarize by saying it seems that for all of the nonclinical models as they may apply to pediatric oncology we have question marks. So, I think collectively we should encourage validation and we should encourage multiple approaches to the models so that we can gain confidence in the models and, by gaining

confidence in the models we can begin to move toward the scenario where the models and the clinical data can be weighted in such a way that we can have a better understanding of what we are looking at.

DR. SANTANA: Yes, I think you said it well. I think while we move towards perfection, if we could ever reach perfection, the systems that we have at hand have served us to some degree and we should not hinder development of any pediatric studies until those models are truly validation and we have the answers to all the questions. I think what we have done up to today has served us to some degree and I think the agency needs to recognize that and deal with each one of the drugs or the compounds or the issues at hand on a case-by-case basis, obviously trying to formalize things in such a way so that everybody kind of does it in the same way until we reach that point of perfection. I think you heard earlier today that it should not hinder our progress until we can validate all these domains and models and come back to you and say this is the best way of doing it. I don't think we are there yet, and I think that is the difficulty of why we struggle with this question.

DR. HIRSCHFELD: Right.

DR. SANTANA: It is very theoretical but we are not there yet. We can give you some examples but we can't give you the whole universe.

DR. HIRSCHFELD: Clearly. So, thank you for those examples. Maybe, in the remaining minutes, we could try to touch on the last question.

DR. SANTANA: Exactly where I was heading. The last question is are there additional recommendations for the effective use of nonclinical data? For example, will open literature reports be generally acceptable? Is documentation of compliance with Good Laboratory Practice necessary to evaluate animal data? Should nonclinical data be submitted as an independent report with a presentation of primary data sufficient for verification and review?

I am going to try to skip to the last one and ask the agency how they would use this verification and review when this preclinical data is being presented. How are you going to judge that data? It is not just that the data is submitted to you, but what tools and what processes will you use to verify and to review the data?

Because I think that will be critical in terms of getting the acceptance of individuals to submit that data--

DR. HIRSCHFELD: Sure.

DR. SANTANA: --whether independent or part of the submission.

DR. HIRSCHFELD: In brief, if we don't have a track record for pediatric oncology it is an open arena so we are attempting to just gain some input into what would be considered acceptable levels of evidence in this regard. We have much more experience in moving from preclinical to the IND phase, but if we are looking for the nonclinical data to supplement clinical data this would be a new area for us. So, we don't have precedents and we can't comment to you, for a variety of reasons, about what we would like to see. We are just trying to get a sense from our invited experts for what you would consider to be acceptable.

DR. SANTANA: Yes, I think the quandary we get into is--

DR. GRILLO-LOPEZ: Clarification, please, acceptable for what?

DR. HIRSCHFELD: Verification of clinical

findings.

DR. GRILLO-LOPEZ: I am sorry to insist on the clarification. Although you don't want to talk about labeling but it is an important issue because you could be saying acceptable for labeling.

DR. WILLIAMS: I might elaborate just a little. I think certainly we do include in our labeling a lot of different pharm tox, biopharm, a lot of different kinds of data and we do accept all kinds of data for clinical use also. The general principles are that, at least for clinical, we often go out and audit but we have sometimes, in circumstances where we have multiple different literature references that all point to the same thing accept the paper. Then, as I mentioned earlier, when we get pharm tox data in we generally like to have data to review and generally, if it doesn't meet the GLP standards, we like people to sort of specify how that differs.

So, I would sort of maybe even propose that in general those same kinds of standards would probably apply to nonclinical data, that if you didn't do it according exactly to our standards you certainly would support it in some way.

DR. SANTANA: Clarify for me, when a

sponsor comes to the agency with an NDA and there is preclinical data there, that data gets reviewed and you already have defined what strategies you are going to use to review that data. What you are implying is that those same parameters would be used for some of these experiments that we are now undertaking.

DR. WILLIAMS: I guess what Steve was saying is when we are talking about a pharmaceutical company that is doing everything under GLP, that is one thing. It looks like in this setting we might be getting different kinds of data that aren't necessarily exactly as pure as that. Recognizing that, I guess to what extent would you go to either compromising or specifying in a certain area certain rules or parameters before you would accept it?

DR. SANTANA: Dr. Smith and then Dr. Helman.

DR. SMITH: Certainly for the contract we are involved with, if FDA has recommendations in terms of reports, we would be glad to consider those and to incorporate those and provide you with reports if those are what the agency needed for a particular consideration.

DR. HIRSCHFELD: I will just address that before Lee speaks. We are asking you today for recommendations because we don't have a position yet. So, that is where we stand.

DR. SMITH: Grant described some kind of characteristics that you might be looking for so we would be open to considering the report formats that would be easier for you to review and be more informative to you.

DR. SANTANA: Lee?

DR. HELMAN: I wanted to ask a question because actually I think it was Dr. Hastings who mentioned this, and nobody has followed up on this and I found it very intriguing, and it follows with some of the information that Chand discussed, which is if we use spontaneous animal models to test the efficacy of a compound and we collected toxicity data, would that be enough if the toxicity data was of high enough quality to not then require additional toxicity data in healthy animals? In fact, I think there is data to suggest that tumor-bearing animals have toxicity that is not necessarily the same as healthy, normal small mammals. I mean, it is something we haven't really discussed, which is the coupling of efficacy data

in pet models and toxicity data, and would that be valid enough to then not require the standard beagle dog or rhesus monkey toxicology?

DR. HASTINGS: Well, first, this is obviously a decision for the oncology division to make about what would be sufficient, but depending on what you knew about the toxicology of a drug to start out with, yes, you might be able to have that as a complete package to support both safety and efficacy. I think the important issue here though--and this is my own personal opinion and I am not speaking for the division, but what we really would like to have, what I would really like to have is the raw data. Remember, GLP is basically a set of bookkeeping rules to ensure the integrity of the study and the validity of the data. That is really what it is all about. Maybe you won't have a quality assurance statement or anything like that, but I think that is what we would want to have in order to know whether or not the safety data you acquired in a diseased animal model, in fact, is valid enough to make a decision about safety in that condition. But I think that, yes, you can get toxicity in, as you said, a spontaneous animal model that actually might be

more relevant to the actual indication than the kind of toxicology data you would get in a healthy animal. Does that answer your question?

DR. HELMAN: To me, it is really a new concept.

DR. HIRSCHFELD: Our approach is that we will be naive and just for a moment pretend there was no FDA and you don't have to ask us how we want it and you are just trying to make a decision. So, you have no clinical data and what we are anticipating is that GLP could potentially be a burden on people so you are going to do something less than GLP and you are going to use it yourself to make decisions and to determine whether the model is good or not good.

So, what we are asking here is, given that GLP could not necessarily be the standard you could practically adapt, what is the standard that you are comfortable with? What would you look at; what would you read that you would say, well, this is valid? So, that is what we are asking.

DR. SANTANA: Dr. Reynolds?

DR. REYNOLDS: Steve, I think the issue, as you hit the nail on the head, is that GLP, which is a very good concept, is not necessarily

adaptable to the academic setting where limited resources are brought to bear especially on pediatrics where resources are limited. Whereas the pharmaceutical industry has the investors to spend those resources, we do not necessarily in the academic laboratory have those.

The problem is when you say less than that, what would we say is acceptable, well, I think everyone in this room can think of examples from the far end of the spectrum of data where you would ask, well, how did that ever get published all the way to data which according to the regulations is not GLP but is what people would be very confident in using for any purpose.

So, what I think we need is not for us as a committee to answer your question, but actually for some guidance from the experts in the FDA that look at GLP issues as to what kind of standards one could apply that are less than full rigor that would be acceptable for the purposes that we want to use these data for.

DR. WILLIAMS: I know that our division commonly accepts things that are not GLP, but we just have the applicant look at the sections of the GLP and tell us how they differ and how they think

they meet the spirit of it. So, I think that is doable. Maybe it could be doable in a more formal setting that met your particular needs for what you are dealing with whether it is tumor models or whatever.

DR. REYNOLDS: Just to finish that, I think this is really important in the concept of what Lee was kind of talking about in terms of using these pet animals, which are fascinating models, because they are never going to make GLP standards. They are actually clinical practice. So, how does one interdigitate those two different worlds into a process that can then be used by the regulatory process?

DR. SANTANA: Dr. Khanna?

DR. KHANNA: There is a little bit of a precedent that is set for drugs that are pursued for the field of animal health and are approved through the Center for Veterinary Medicine within the FDA. The issues that we deal with there are basically the availability of raw data, the contemporaneous keeping of records, and the use of standardized tests and measures against those animals.

So, speaking only to the use of the pet

animal studies, there is a body of regulations that oversees these trials and, in fact, those same guidelines which are more GCP-like may be very useful in studies in mice, and they are not as onerous as GLP, and there are probably areas for modification but they may be a good resource to look at.

DR. SANTANA: Dr. Adamson?

DR. ADAMSON: Steve, I think there are really two scenarios. One is that there are observations made by an independent laboratory that hadn't necessarily set out to generate the data that was going to go to the agency but that is important data. There, I think the scientific method is a pretty robust one. That is, it undergoes peer review and if it is important someone ought to repeat it and show the same thing. I would hold any of those observations to the same standards. I mean, if something is not reproducible by another laboratory, it is not to say throw it away but it should raise some questions.

I think what we have been spending more time on is, okay, we are undertaking a program, the sole objective of which is really to provide

guidance for drug development. There, I think if you have a standardized approach where the methodology is well described and there are standard operating procedures--again, it isn't GLP but it isn't the opposite of GLP but it is several steps toward it--and I would love to hear Peter Houghton's opinion on this--but I think it would be reasonable to get access to the raw data. Because usually the limitation of GLP is manpower and resources, and if it is important and we can do a data dump and someone else at the agency can crank through it to see if we get the same results, I think that is a reasonable approach.

DR. HIRSCHFELD: Dr. Hastings, there is a seat there with a microphone and you can take that, and I will just clarify the question. When we said primary data, that is synonymous with raw data; that is unprocessed data.

DR. HASTINGS: Right. I just want to make one point. Actually, we have talked about the pet--well, the companion animal studies. I believe that under the regulations if you do an experimental study in companion animals or pets you have to have an IND with the Center for Veterinary Medicine.

DR. KHANNA: I will just briefly respond. That is not necessarily true. It depends on the basis around which you are trying to pursue the drug. If you are pursuing that drug for a veterinary indication it needs to go through the CVM. If you are not, the CVM has told us that they would not want to be involved in the review of that data that is going towards the human development of a drug. In fact, they request from us to get regulatory discretion from the human side.

DR. HASTINGS: So, you have already discussed that with CVM?

DR. KHANNA: Yes.

DR. HIRSCHFELD: I can just verify that I was specifically involved in a case or consulted where it turned out to be Dr. Khanna who was submitting a protocol and we were asked whether this was going under an IND that existed for human studies, and we were able to verify that, yes, it was under an IND for human studies and that the data would feed into the collective pool of data for understanding the potential human application and then the Center for Veterinary Medicine gracefully withdrew.

DR. WILLIAMS: It seems like a small

working group between the Center for Veterinary Medicine and FDA and oncology groups especially could work out some kind of formal/informal arrangement.

DR. SANTANA: Yes, I think that would be critical because as this experiment unfolds over the next few years we want to make sure that the data that we are collecting, and the way we are collecting the data will be acceptable to the agency because, if not, we are going to be faced with the issue of how do we advance drug development in children if the data, for one reason or another, hits a regulatory snarl and is not accepted by the agency. I think Donna had a question or a comment.

DR. PRZEPIORKA: Yes, for the record, if an academic institution participates in a trial that goes to the FDA, the FDA can come and audit that academic institution to make sure their clinical trial was done appropriately. If an academic laboratory has their data used to support an IND, is that laboratory open for being audited by the FDA as well?

DR. HIRSCHFELD: The data from that study would be, and we have had circumstances where there

were, let's say, perceived irregularities in data from a laboratory under a number of INDs and what we have done is for-cause inspections of that facility. But if it is a single study that an academic laboratory is doing and the data appear to be internally consistent and robust, that usually is not a trigger for an audit.

DR. SANTANA: Dr. Grillo?

DR. GRILLO-LOPEZ: In the setting of an existing NDA, that is a product that has been approved let's say for an adult malignancy, that NDA is a pharmaceutical company's NDA that has been submitted to the FDA and obtained that approval. Usually the way the data works its way into that NDA and the overall database is through the pharmaceutical company. So, one way that your data would get to the hands of the FDA would be through, in this case, this third party pharmaceutical company that then transmits it to the FDA and the FDA will ask for the raw data. In fact, in pharmaceutical companies we practically always submit the raw data to the FDA in addition to all analyses and interpretations, etc., with some exceptions where a publication might be sufficient for some particular purpose. So, in many

situations you would be working with the pharmaceutical company to put data in a format that would be acceptable to the FDA unless you held your own IND, and then you would file the data to your IND, if I am correct.

DR. HIRSCHFELD: Right, and again we are not restricting it to the NDA filing final phase of development but we are opening the whole discussion to all aspects of product development.

DR. GRILLO-LOPEZ: Yes, I understand but I just wanted to make the point again, as I did earlier this morning, that as we are conducting this discussion it is missing one leg of the stool. I am the only industry representative around this table, and to make this discussion more effective we should have had other industry representatives and presenters who are more expert than I on pediatric oncology.

DR. SANTANA: Dr. Grillo, noted again in the discussion of the afternoon of that issue. Susan, you had a comment?

DR. WEINER: Yes, I guess I wanted to tie it to the discussions earlier in the day from the public's perspective, from the family's perspective. That is, the most valuable resources

I think that we all have in this situation are the patient resources, the number of kids who are involved and their well being and time. Insofar as the conduct of any preclinical or nonclinical activity is done for its own sake or is done without it being in direct service of advancing therapies for kids, I think we have to question that and be mindful of that.

In addition, I think it is very important that the agency, when they consider what they require of sponsors or what kinds of studies they believe should be done on kids given what has happened in the preclinical setting, the notion that resources have to be conserved--that risk has to outweigh benefit, to be sure--but that resource have to be conserved because they make commitments into the future that may not be necessary I think is vital, and it is a vital selling point to the families community to hear that from you and I appreciate the exquisite nature with which the discussion is taking place.

DR. SANTANA: I think that is a very good concluding comment for the discussion this afternoon and I couldn't have said it any better. So, unless the agency requests that we provide any

further comments, I think we have attempted to give you the best that we could, given what we were asked to comment on. So, I want to thank everybody that participated. I know it was a tough discussion this afternoon because it was more theoretical based rather than practice based but, hopefully, in the future, once we get more data, we can probably relate it to more practical issues at some future point.

DR. HIRSCHFELD: And I want to thank all of you for helping us. We could say that we are at the edge and trying to push it but we don't even know where the edge is, and I thank all of you for helping us explore the unknown with the hope that the future will be the known, and our gratitude is noted too.

DR. SANTANA: Thank you, Dr. Hirschfeld.

[Whereupon, at 5:10 p.m., the proceedings were adjourned.]