UNITED STATES FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ETHICS SUBCOMMITTEE MEETING

OF THE PEDIATRIC ADVISORY COMMITTEE MEETING

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Monday-Tuesday, September 9, 2013

Hilton Rockville Executive Meeting Center

1750 Rockville Pike

Rockville, Maryland, 20852

The meeting was convened at 8:00 a.m.,

JEFFREY BOTKIN, M.D., Acting Chairman, presiding.

MEMBERS PRESENT:

JEFFREY BOTKIN, M.D., ACTING CHAIRMAN, PRESIDING

VICTOR SANTANA, M.D.

† AMY CELENTO, B.S.

JOHN BRADLEY, M.D.

ROBERT DAUM, M.D.

LEONARD GLANTZ, J.D.

NORMAN FOST, M.D., M.P.H.

LORETTA KOPELMAN, PH.D.

STEVEN JOFFE, M.D., M.P.H.

JOHN GRABENSTEIN, R.PH., PH.D.

STEVEN KRUG, M.D.

THERESA A. O'LONERGAN, PH.D., M.A.

TOMAS SILBER, M.D.

PHILLIP PITTMAN, M.D.

BENJAMIN WILFOND, M.D.

ALSO PRESENT: WALTER ELLENBERG, Ph.D.,

MICHELLE ROTH-CLINE M.D. Ph.D.

Executive Director and Designated Federal Official

† Acting Patient-Family Representative
# Industry Representative

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P R O C E E D I N G S

(8:05 a.m.)

WELCOME AND INTRODUCTORY REMARKS

CHAIRMAN BOTKIN: Well, good morning, everybody. I'm Jeff Botkin from the University of Utah, and my thanks to the FDA for the opportunity to be at what is going to prove to be a fascinating discussion today. So I have the opportunity to chair the meeting. So what I thought I would do first thing this morning is just go around the table here and ask everybody to just give themselves a sentence or two of introduction. And then Dr. Ellenberg will give us some information. I'll then provide a few basic background comments based on some of the materials we've gotten. And then we'll launch into a series of presentations this morning.

Dr. O'Lonergan.

DR. O'LONERGAN: Terry O'Lonergan. My background is in pediatric research. I'm currently the Director of Research Compliance for Catholic Health Initiatives National.

DR. WILFOND: Good morning. I'm Ben Wilfond. I'm the director of the Treuman Katz Center for Pediatric Bioethics at Seattle Children's Hospital, and also the University of Washington. And my clinical background is in pediatric pulmonology.

DR. KOPELMAN: Good morning. I'm Loretta Kopelman. My degree is in philosophy. I'm professor emeritus at the Brody School of Medicine and faculty affiliate at the Kennedy Institute of Ethics at Georgetown University, where I currently teach.

DR. BRADLEY: I'm John Bradley. I'm a pediatric infectious disease doctor, and I've been doing clinical research and clinical practice since the late '70s, and have seen profound changes based on some of the research we've done with both drugs and vaccines. And I would like to continue to add effort going forward. And it's a privilege to be here. Thank you.

DR. NELSON: I'm Skip Nelson. I'm the Deputy Director and Senior Pediatric Ethicist at the Office of Pediatric Therapeutics at the FDA. And my clinical background is Critical Care and Neonatology. And for those who haven't asked, I fractured my right clavicle on Saturday while bicycling. I was wearing a helmet.

DR. ROBERTS: I'm Rosemary Roberts. I am the director of the Office of Counterterrorism and Emergency Coordination at the Center for Drug Evaluation and Research, FDA. My background is in pediatric infectious disease.

MS. KELLEY: Good morning. Cynthia Kelly, Senior Advisor for Counterterrorism, Medical Countermeasures at the Center for Biologics Evaluation and Research, FDA.

DR. GRABENSTEIN: I'm John Grabenstein. I'm the designated visitor, I think. I am a pharmacist and epidemiologist. I lead the medical affairs group for Merck vaccines up in Philadelphia. I think the reason I'm here is that in a previous life, when I was in the Army, I led the Department of Defense Anthrax Vaccination Program for seven years, and more recently was a member of the National Biodefense Science Board panel that issued a report on pediatric use of anthrax vaccine. I called myself its librarian for knowing the literature.

DR. KRUG: Good morning. My name's Dr. Steve Krug. I'm a pediatric emergency physician. I'm a professor at the Feinberg School of Medicine, and I head the Division of Emergency Medicine at the Ann and Robert H. Lurie Children's Hospital in Chicago. I have my hands in lots of different things and have been involved in clinical research in the emergency care setting. One of my great areas of interest is emergency preparedness. And I am honored to be here.

DR. DAUM: Good morning. I'm Robert Daum. I'm a pediatric ID guy also at the University of Chicago. About a year ago, or a little over, I broke my arm and was in a sling

for a long time, which is why I had a special visual phenomenon with Skip over there wearing a sling now. I have a vaccine past where I chaired the FDA's Vaccine Advisory Committee once, and then got asked to do it again. I said yes. And I also work on Staphylococcus aureus infections in the lab.

DR. JOFFE: I'm Steve Joffe. I'm a pediatric oncologist and bioethicist with a particular interest in research ethics. I'm at the University of Pennsylvania School of Medicine.

DR. GLANTZ: I'm Leonard Glantz. I'm a lawyer. I'm on the faculty of the Boston University School of Public Health and the Boston University School of Law, and old enough so that I wrote one of the legal background papers for the original National Committee on the Protection of Subjects.

DR. FOST: I'm Norm Fost, Professor of Pediatrics and Bioethics at the University of Wisconsin, chair of the IRB for 37 years. My application to the Guinness Book of Records is still pending.

[laughter]

DR. SILBER: Hi, I'm Tomas Silber. I'm the director of the Pediatric Ethics Program at Children's National and the director of the Regulatory Section of the CTSI, and vice chair of the IRB there. My clinical background is adolescent medicine.

MS. CELENTO: Amy Celento, patient and family representative.

DR. SANTANA: Good morning. I'm Victor Santana. I'm a pediatric oncologist from St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. ELLENBERG: Good morning. I'm Walt Ellenberg. I'm the designated federal official with the Office of Pediatric Therapeutics at FDA.

CHAIRMAN BOTKIN: And I'm Jeff Botkin, General Pediatrician, University of Utah. I have been doing bioethics for about 20 years, and the associate VP for research there. And currently chair of the Secretary's Advisory Committee on Human Research and Protections. So, a real privilege to be part of terrific group here. Many folks around the table have had longstanding major contributions to the literature on pediatric research ethics, so I'm particularly looking forward to what should be a wonderful discussion about these issues.

I'll make a few other very brief introductory comments, but I want to turn it over to Dr. Ellenberg.

DR. ELLENBERG: Thank you. Good morning to the members of the Pediatric Ethics Subcommittee, the invited speakers, FDA staff, and members of the general public. We welcome you to this important meeting.

The Pediatric Ethics Subcommittee of the Pediatric Advisory Committee is meeting today to discuss ethical issues and pediatric product development, including medical countermeasures, focusing on the concepts of minimal risk, disorder or condition, and exposure of pediatric subjects to risks under 21 CFR 50.54.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that those individuals participating in the meeting do not have a financial interest that presents potential conflict of interest.

Subcommittee members are reminded that they have only been screened for conflicts of interest concerning FDA-regulated products for the prevention and/or treatment of anthrax, including raxibacumab to treat inhalation anthrax. Given the complexity of the topics that will be covered, this meeting has been structured as a non-voting discussion, and the subcommittee members may wish to illustrate points using case examples drawn from their experience with the development of pediatric products, or more specifically, pediatric medical countermeasures. However, focus of the discussion should remain on the general ethical concept being illustrated by the case rather than the case itself.

In general, the committee participants are aware, then, of the need to exclude themselves from involvement in the discussion of topics if their interest would be affected, and their exclusion would be noted for the record. Subcommittee members must declare whether or not they have any conflicts of interest when using non-anthrax case examples to illustrate a general point.

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

We have one open comment period, or open session, which is scheduled today at 2:00. If you're planning to make a public statement during this period, please make sure that you sign in at the registration table.

I'd also like to remind everyone at the table to, when you get ready to speak, please turn on your microphones and raise your hand so we can acknowledge you. And then when you're finished, to please remember to turn off the microphones because we can only have a certain number open at any given time.

Finally, I'd like to remind everybody in the meeting, including committee members, to silence or turn off your cell phones and Blackberrys so that we avoid any kind of interruptions.

And then the last bit of information that's important to this is that as a subcommittee, the ethics subcommittee is linked to the Pediatric Advisory Committee, and therefore we have to have representation at this meeting by members of the Pediatric Advisory Committee. I'll let you know that Dr. Santana, to my left, and Ms. Celento, to my left, are standing members of the Pediatric Advisory Committee. And that concludes my comments. And I appreciate your attention.

CHAIRMAN BOTKIN: Thank you. Well, that touches on some of the issues I wanted to touch on. And basically, the background is such that we don't have an application, per se, that we're addressing. So we want to be speaking about these issues at a certain level of abstraction that will guide policymakers on these types of issues as these problems come forward in the future. Certainly a possibility that we may reconvene at some point around a specific application, but that's not today's task.

My job, as part of the agenda, is going to be to try to walk us through the specific questions that have been posed to us, try to garner as much consensus as we can on each of the issues while making sure that the notes adequately reflect any differences of opinion that may emerge in the discussion.

Quite a few questions that have been posed to us: We have some background presentations first, to frame some of the

issues, and then a series of questions we'll walk through for the next day and a half or so. So we'll need to be relatively concise while trying to provide some substantive guidance on some longstanding and profound issues in pediatric research ethics.

So, I think with that, let's proceed on with the agenda. And what I've been provided is some introductory material for each of our speakers over the next day. So before they speak, I'll go ahead and read through verbatim the background information that they've provided. And then we'll go from there.

So our first speaker is going to be Skip. Robert Skip Nelson, M.D., Ph.D., is currently the Deputy Director and Senior Pediatric Ethicist in the Office of Pediatric Therapeutics, Officer of the Commissioner at the U.S. Food and Drug Administration. Prior to joining the FDA full time in 2009, he was Professor of Anesthesiology, Critical Care, and Pediatrics at Children's Hospital, Philadelphia, and the University of Pennsylvania, School of Medicine.

So thanks, Skip. And thanks for all the work that you put into the background for this meeting. Skip.

OVERVIEW AND GOALS FOR THE MEETING

DR. NELSON: Thanks, Jeff. Can you hear me? So Walt already mentioned some of this, but basically we are going to be talking about three particular topics: minimal risk, disorder or condition, and exposure of pediatric subjects to risk under 21 CFR 50.54.

Now, the context for this meeting, just as a reminder, is that over the last, now almost two years, there has been an ongoing discussion about anthrax testing in the pediatric population, with a report issued in October of 2011 from the National Biodefense Science Board, then a charge to the Presidential Commission for the Study of Bioethical Issues by Secretary Sebelius to look at these issues. We held a report at which some of you were participants. John was one of our scientific rapporteur, and Steve, I think, was our ethics rapporteur. So we had a broad-ranging discussion of some of the ethical and regulatory considerations in pediatric medical countermeasures. And then, of course, in March, the Presidential Commission released their reports.

So there's certainly a lot of discussion that's been going on over the last two years. But I do want to emphasize that we're not really being asked to assess any of the specific recommendations in the Presidential Commission report, nor to

opine on whether a particular trial should or shouldn't be done. That's not really our purpose today.

The idea is for us to sort of take a step back and look at three important concepts within Subpart D that guide the ethical protections for children in research, and to discuss those within this context, but discuss them in a way that would provide guidance overall on Subpart D in FDA-regulated clinical investigation. So there might be a specific context that has brought us together, but I think what we're discussing today would have much more general applicability as well. And that's particularly why I am interested in the discussion.

Now, Walt had already mentioned the case examples. Honestly, the questions we've put to you are fairly conceptual, and it's difficult to talk about concepts without having some cases at hand. There certainly are the cases of anthrax that have been discussed over the last couple of years. And you've all been screened for conflict of interest around that. But you may or may not want to bring up other cases to illustrate general points. But the issue is that we are not going to then go discuss at that case, per se, but we'll be discussing the general point that you're illustrating that with because none of us have been screened for conflict of interest around other cases.

So I don't want to inhibit you to say, "Well, for example," but on the other hand, we then need to move off that example and talk about why you felt it was an illustration of the more general point.

Now, I'm not going to walk through these questions, because it would take up too much time, and I'd like to basically just highlight them. But, if I might say, in effect, question one will answer all of the problems about minimal risk that have been debated over the last 20 or 30 years.

[laughter]

So if, in fact -- [laughs] -- if, in fact, you answer those questions, I'll be fascinated. But that's the point. It's really addressing it.

So the first question is, what activities of daily life should we consider? And you'll see the definition of minimal risk in a later presentation. But it involves daily life. What activities of daily life should we consider? And these are "please consider the following points." And so these, in a sense, are not necessarily sequential, although I tried to put them in some logical order. So that's the first question.

The second is that there have been recommendations that this should be indexed against average, healthy, normal children. Institute of Medicine recommended that. Secretary's Advisory Committee recommended that. So this is an opportunity

for you all to discuss that qualifier and the implications of that qualifier.

The next would be is there a morally relevant difference between whether the risk a child is being exposed to in daily life or in research, as opposed to a simple comparison? Are there morally relevant differences in the purpose of that activity? And then what factors would you consider? And then there's a discussion in the literature about trying to capture the normative or value-laden component of minimal risk with some different suggestions that have been proposed. And this is an opportunity for you to talk about those suggestions, one of which is charitable participation. The other is scrupulous parent.

And then finally, should minimal risk depend upon age or developmental stage? There's nothing in the definition, per se, that states that. So that gives you the range of issues in minimal risk that I am proposing you discuss. And I might also say we've allotted two hours for each topic. But that is a rough guess. I mean, if one takes more or less than the other, that's fine. I think Jeff and the committee can use their judgment about where they spend their time, and not be held to that as an absolute requirement if one topic takes more.

Second is disorder or condition, which is not defined in the regulations. There are definitions that have been

proposed, one by the Institute of Medicine, one by SACHRP, which is a minor modification of that. But how do we understand this? What criteria or characteristics of children should we use to identify them as having a disorder or condition?

There are some arguments that certain group characteristics are inappropriate to consider, exposure to violence and so on, that would say a child might be at risk. And so this would be an opportunity for you to say, "Well, what are the issues that we should think about if certain characteristics would not be appropriate to say a child is in a condition that would warrant exposure to more than minimal for non-therapeutic research?"

And then, finally, this notion of condition is understood, at least in these definitions of saying children are at risk for certain things. How do we understand what that means? How do we understand that a child might be at risk for it? May not have the condition now, may not have a disease now, if you will. But how do we understand them being at risk?

So that explores. And then there's this other question of vital importance for understanding amelioration. Does this influence one's understanding of disorder or condition? So that's the second topic.

The third topic is what I call my stretch ethics topic, which is, are there circumstances under which we could

expose children to more than a minor increase over minimal risk absent the prospect of direct benefit. And if so, what would those be? Any thinking about that? Would that be influenced by the degree of uncertainty, about the future use of a product, the degree of uncertainty about the potential risk a child may be exposed to? How do we understand uncertainty in that context? And I point out in this question that we often understand pediatric medical countermeasures as being more than just simply a response to some sort of intentional threat, if you will, of a weaponized agent, but could also be understood in terms of natural events or diseases that may not be common but such as pandemics and the like. So it's not as if this is an opportunity to think more broadly, if you will, about our understanding of uncertainty.

And then, finally, the magnitude of harm --

OPERATOR: -- is now joining.

DR. NELSON: I think that means the CDC has just come on the phone, right, Walt? Okay. And welcome.

So, basically, those are the questions. And then finally, those who know 50.54, and you'll hear talk about this, understand that the data needs to be discussed in public. And so, what does it mean if, in fact, the risk of certain events happening would be based on the understanding of sensitive information. How would that sensitive information be made

public? So this is an opportunity for you to comment on that public requirement for a public panel under 50.54. And how do we understand that within the context of this kind of ethical review?

So, what I've walked you through is, the idea is behind the questions that I framed, not the words themselves. My recommendation is that you have that in front of you and you can then post that. They are in the background document. And you can then also post it as you get to the discussion themselves. But I didn't want to just read through them, but give you a flavor of the kinds of issues that we are going to be discussing over the next day and a half.

And I will say I'm looking forward to what you have to say. And I know these are not easy questions, and they're not meant to be. And it'll be interesting to see what you all have to say about them. So, thanks.

CHAIRMAN BOTKIN: Thanks, Skip. Any specific questions for Skip before we move on? Okay, very good.

We next have Michelle Roth-Cline, who's going to provide us an overview of the ethical framework for 21 CFR 50 subpart D. Dr. Michelle Roth-Cline's on the FDA's --

OPERATOR: -- is now joining.

CHAIRMAN BOTKIN: -- Office of Pediatric Therapeutics in 2009 and is pediatric ethicist and health scientist. Her

responsibilities include coordinating a busy pediatric ethics consultation service, available to any review division within the agency, providing training in pediatric ethics to agency reviewers, and participating in the development of a guidance documents in many aspects of pediatric research. Good morning.

OVERVIEW OF THE ETHICAL FRAMEWORK

OF 21 CFR 50 SUBPART D

DR. ROTH-CLINE: Thanks, Jeff. Good morning. Thanks to everyone for being here.

I just want to proceed with a discussion of the basic ethical and regulatory framework for the topics we'll be discussing this morning. So as an introduction, we'll talk about some basic ethical principles, the ethical framework; talk about justification for research risk and how those ethical principles have been incorporated into our regulatory scheme; talk about the lower risk pathway, the higher risk pathway, and the escape hatch, and I'll explain what all of those are; key concepts in the lower risk pathway; and then federal panel review under 50.54, and some of the previous recommendations.

So I don't think I have to explain to this committee why pediatric research is important. That is, we want children to be able to enjoy the same access to safe and effective medications at appropriate doses as adults or anyone else in this country.

So I think over the past 15 or so years, we've evolved from a view that we must protect children from research, to a view that we must protect children through research. And we, as clinicians and regulators, have a professional obligation to ensure that there are adequate data to support the safe use of

drugs and biological products in children. But also, we want to make sure that children that only enrolled in research supporting that goal that is both scientifically necessary and ethically sound. And, as well, children are widely considered to be vulnerable persons who should be afforded additional protections in research.

OPERATOR: -- is now joining.

DR. ROTH-CLINE: As I mentioned, the basic ethical framework in pediatrics have sort of tried to distill into five main principles, if you will. And I think there's pretty wide agreement internationally on a lot of these. The first is the principle of scientific necessity; that is, children should only be enrolled in the clinical trial if the scientific or public health objectives can't be met by enrolling subjects who consent for themselves. And absent a prospect of direct therapeutic benefit, children should only be exposed to low risk. And we will talk about what those are.

Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care. The fourth is the one principle that is perhaps more unique to our particular regulatory scheme. That is, research protocols that are not approvable using standard processes should be subject to full public discourse and debate in order to determine whether

they should proceed, and that is what this committee is for and has done in the past. And fifth, vulnerable populations who are unable to consent for themselves, including children, should have a proxy to protect them, in this case typically parents or guardians.

So I will be referring back to these principles through the presentation, but I wanted to talk a little bit more about the principle of scientific necessity. We derive this from the requirement for equitable selection, and the regulatory citation there is below. That is, subjects who are capable of informed consent should be enrolled prior to children. I think most of us think of the requirement for equitable selection as equitable selection in terms of race, or gender, or something like that, but I think if you look back at the work of the National Commission, they've very clearly had this idea in mind of adults before children. And that's a prima facie obligation, that is, a rebuttable presumption, perhaps, that there are circumstances in which we might enroll children before we enroll adults. But I won't get into that more today.

So the practical application here of the principle is to try to determine the type and timing of clinical studies required to establish the safe and effective pediatric use of products, or, in the case of FDA regulated products, really to label them.

So I'm going to go on here to talk about the justification of research risk. So, in general, the justification of research risk is found at 21 CFR 56.111, and that is, risk to subjects are reasonable in relation to the anticipated benefits, if any, and to the importance of the knowledge that may be expected to result from the research. This general criterion is modified by the additional protections for children to cap the risk to which children should be exposed for the sake of knowledge. And in many ways, the additional protections for children can be thought of by sort of lumping them into these pathways as I was talking about before. That is research involving children must be restricted to low risk minimal or a minor increase over minimal risk absent to potential for direct benefit to the child. This was principle number two that I talked about upfront. Or the research must present risks that are justified by the anticipated direct benefit. That's principle three. Or research must be reviewed by a federal panel.

So you can see how the basic ethical principles that have then been incorporated into our regulations, and this is just a list of the additional safeguards with which you're all familiar. One of the ways, if we go back here, that we delineate whether research falls into different paths is whether or not there is a potential for direct benefit to the child.

And so I want to talk a little bit about what direct benefit means.

And I will say this committee has opined before on what direct benefit is and means, and so what I'm saying here is perhaps a majority view on what it means, not that we are all necessarily in agreement. But a majority view of direct benefit is that the benefit accrues to the individual subject or the individual child enrolled in a clinical trial, results from the research intervention being studied and not from other clinical interventions, and the word benefit is often modified by clinical benefit or medical benefit to indicate that the direct benefit relates to the health of the child. And then other things, that the direct benefit is really based on the nature of the intervention and not the intent of the investigator and so forth.

So this is where we really link science and regulations and ethics. So the determination as to whether one goes down a lower risk pathway or a higher risk pathway is really based on data. That is, a lower risk pathway, if there's no prospect of direct benefit, if we don't have data to establish a sufficient prospect to direct benefit, the low risk pathway says that the administration of the investigational product must be low risk. The higher risk pathway, that is, we can tolerate higher risks if there is a prospect of direct

benefit that is sufficient to justify those higher risks. We have talked about this pathway in the past. We have talked about prospect of direct benefit. I am not going to say a lot more about it today because a lot of the concepts we're focusing on are really either in the lower risk pathway or the escape hatch, which we're getting to, which is the 50.54 process. That is studies that really do not fit into either pathway.

So, key concepts in the lower risk pathway. That is, absent prospect of a direct benefit studies or procedures fall into three possible categories. The first is minimal risk, or a minor increase over minimal risk, or studies that don't fit these criteria can be referred to a federal panel. As I mentioned, the application of the lower risk pathway depends on whether we have data to establish the risk level. If we don't, typically we would think of referring those to a higher risk pathway.

So normal or routine risks: We want to talk about defining minimal risk to sort of help you on your task today. The National Commission defined minimal risk as "those risks that are normally encountered in the daily lives or in the routine medical or psychological examination of healthy children." The phrase of "healthy children" was actually not included in our regulations whenever our regulations were codified from what the National Commission wrote. However, most

ethicists in U.S. federal panels, the Secretary's Advisory Committee, IOM, and so forth, do agree with this limitation.

Children without any health conditions therefore could be exposed to interventions are procedures that are approved as minimal risk. So, generally, I think, though, the administration of experimental products is not normal or routine and it's not something we typically do to healthy children, and so we don't generally think of these as being minimal risk.

Minor increase over minimal risk: There's, again, no definition of what this means exactly in the regulations. Descriptions of this level include slightly more than minimal risk or no substantial risk of illness or injury. These were what the National Commission proposed. The SACHRP, the Secretary's Advisory Committee said, "The associated harm should be transient and reversible." Research under the minor increase over minimal risk category has a couple of additional stipulations, and the first is that it should present experiences to the enrolled children that are reasonably commensurate with other experiences in their life and as well be likely to yield generalizable knowledge about the subject's disorder or condition. And this is where we get into the disorder or condition requirement that Skip mentioned earlier.

Again, disorder or condition isn't defined. The proposed definition that we have up here as Skip mentioned that

the IOM proposed is a set of specific characteristics that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future. So there's a key concept here, which is being at risk for a disorder or condition, and I think all of us understand what it might mean to be at risk for, say, diabetes or something like that. I think it is a different question perhaps, and you can help us answer this, as to what it means to be at risk, let's say for inhalational anthrax. Are we at risk for the kinds of the things in the medical countermeasure field?

And I will say as well that the presidential commission in their report specifically did not consider disorder or condition because they didn't find it relevant to the intentional exposure, perhaps to a bioterror attack. In other words, a bioterror attack would be intentionally exposing people to this. So they didn't talk about this issue of disorder condition.

So, as I said, this low risk pathway may have applicability depending on the product, but perhaps not a lot. We must be able to generate an accurate risk estimate given adult testing experience if we're going to apply the low risk pathway to pediatric product development. We can use it for

low-risk procedures used for drugs if ample data exists to establish that the risk of use is low.

Finally, I'm going to talk today about federal panel review under the 50.54 process. So the National Commission, originally, when they were creating the principles that now are in our regulations, created first this minimal risk, this idea of minimal risk research, or research that has a direct benefit. But they were concerned, once they created these two categories, that important research that may present greater than minimal risk without any compensating benefit might be excluded if those were the only two categories of research that was allowed. And so hence there was this sort of "escape hatch," quote, unquote, that was developed. Early themes for use of this escape hatch were a grave public health concern, full disclosure and debate, that adequate protective measures could be developed for children in this case, and examples discussed at that time included polio in the 1976 outbreak of swine flu. So the focus, then, of their subsequent discussion was to define criteria for use of the escape hatch and to clarify the process.

So there was a recommendation for a National Advisory Board, and that is what created this subcommittee, and was incorporated into our regulations at 21 CFR 50.54. And you can see here the criteria for approval in a clinical investigation. That is it presents a reasonable opportunity to further the

understanding, alleviation, or prevention of a serious problem affecting the health and welfare of children. It involves a panel of experts. There's an opportunity for public review and comment. The study will be conducted in accordance with sound ethical principles. And again, adequate provisions are made for soliciting the assent and permission. So this National Advisory Board was established in 2003, and you have served us well in that regard.

So the implementation: You have reviewed four protocols since this public review was established in 2003, and you can see the topics here. The common theme for the first three protocols was administration of an intervention that presented a minor increase over minimal risk to children who did not have any disorder condition, that is, to children who are perfectly healthy.

The fourth protocol, this GCSF study here, I want to talk a little bit more about. So the selected findings here, and there's some of you who will probably remember this, that risks of GCSF administration represented more than a minor increase over minimal risk. Therefore, the protocol was not approvable for the healthy sibling donors using 50.51 or 50.53. Any benefits to the healthy sibling donor were considered indirect. So therefore, the protocol wasn't approvable as a prospect of direct benefit because, again, there was no direct

medical clinical benefit to the healthy children who were enrolled. But the inclusion of healthy sibling donors was felt to meet the criteria for approval under the 50.54 process that I just talked about a couple of slides ago here. So what I want to point out is that a precedent actually exists under which this committee has recommended the approval of a study on healthy children that poses more than a minor increase over minimal risk with no prospect of direct benefit.

So these are reflections on the escape hatch by the National Commission. The ethical principles at stake are the moral obligation to protect the community or to come to the aid of certain sufferers within it and the moral prohibition against using unconsenting persons at considerable risk to their well-being for the promotion of the common good. These principles are of such moment and their observant so direct, so basic to a just and human society, that any debate about their application should be held at the most public level of discourse. And as I read this in preparation for this meeting, it occurred to me that what we are asking you to do today is to discuss three concepts that will shape our application of fundamental ethical principles to pediatric product development and as well inform those of us who will be creating draft guidance on 21 CFR 50 Subpart D. And I will say, as Skip did, if as well you are able

to settle the debate that has raged in the literature for the past 30 years on minimal risk, God bless.

Thank you very much. Are there any questions we can address?

DR. BRADLEY: Thanks very much for that excellent overview. Having worked with Skip over the past couple of years on many of these issues with medical countermeasures and having read all the materials, the discussion about minimal risk and minor increase over minimal risk seems to run up against the tension of medical countermeasures. So the issue of inhalation anthrax somehow being equated to events of everyday life and risks just seems to be disconnected, and as we look at medical countermeasure research, whether it's for an antidote for sarin gas or a dirty bomb nuclear radiation thing where testing antidotes in otherwise healthy kids would need to occur if there were a medical countermeasure, and looking that the CFR, this 54 was posted on April 24th, 2001, before the 9/11 attacks, it seems as though the discussion on minimal risk, which is very critical, takes on a completely different connotation in the context of medical countermeasures. And as was mentioned, even the Presidential Commission on Ethics that talked about anthrax vaccine wanted to disconnect themselves.

So somehow in our discussion, I keep wanting to disassociate risks for regular research and risks for medical

countermeasures because there is such a more profound level of injury and death with medical countermeasures that it's almost inconceivable to put those risks and effects together with those that we encounter every day. Even influenza, we get notice that the influenza is starting in one area of the world then spreading. Not that that's going to be easy, and obviously the intelligence community has information on what the risks are of a bioterror event that we normal humans won't ever get a chance to see, which is probably a good thing.

But since the purpose of these discussions today and tomorrow are going to center around medical countermeasures, I keep wanting to disassociate medical countermeasure discussions from discussions of drugs for otitis media and strep throat and stuff like that. I was on the FDA Anti-Infective Drug Advisory Committee when telithromycin was being used for otitis, and there is a slight increase in liver toxicity, so all the otitis protocols got shut down because it wasn't found to be worth it. But with medical countermeasures, whether it's radiation, chemical, bioterror, the results are so profound that to discuss minimal risks compared to everyday life, "What is the risk of falling off a bike," it just doesn't compute. There is a tension there, so I don't know how to carve out medical countermeasures and I'm happy to put them in any of the categories, 52, 53, or 54. I'm not trying to propose that. But

not try to lump medical countermeasures in with all the other research that we do. Thank you.

CHAIRMAN BOTKIN: Good, thank you. Well, that's good challenge for us, and I think the concept as I draw is the question about whether we can look at these new challenges from extrapolating from more familiar context or whether we need to sort of re-think some of these concepts in the context of this less familiar circumstance.

DR. SANTANA: So, John, let me see if I follow you. So you're trying to advocate that there should be a completely different framework for evaluating issues that relate to medical countermeasures research in children. Is that where you're going?

DR. BRADLEY: Well, not completely, but yes, a separate category. So there's regular pediatric research and then medical countermeasures, by definition, have a risk of occurring which is not known to the general public, and probably, for security reasons, can't be known. So we can't debate what is the likelihood, how can we compare daily events with medical countermeasures? So it takes it out of the realm of debate.

Now if you want to get a select committee and get them top security clearance and put them in a room and educate them and then debate it, that would work. But I think lumping it

together with general research, we're never going to get an answer for medical countermeasures.

CHAIRMAN BOTKIN: Dr. Krug.

DR. KRUG: Yes, hi. Just to sort of build on John's point, one of the challenging issues here is the estimation of risk, and I've seen a variety of groups. I sat at two of the presidential commission meetings and I'm on the MBSB. I don't really know what the risk is. And I think thoughtful clinicians, ethicists, and others when they look at this and they're trying to go through a framework understanding the balance between benefit and risk, it is impossible to estimate the risk.

What little I know about weaponized bioagents and various other bad actors is that they can be very lethal. The question is, will it ever happen? One could say it's happened in other places, it's happened in small scale. So that's where this framework falls apart. So I'm actually very much on the same page as John, which is it's hard to sort of understand normal daily living as it reflects to the risk of bioagents because it might never happen. I mean, 25 million children seek emergency care every year, so emergency departments happen for otherwise healthy kids.

But I think in order to understand the perceived benefit in determining whether any trial for any countermeasure

somehow fits either is minimal risk, slightly more than minimal risks, or fits within the escape hatch as its been described, and/or whether it fits within the, and I'm going to quote something that was said, the "moral obligation to protect the community," I think if we're ever going to get to an answer to the question on this particular topic, I think we sort of have to kind of formulate risk and/or an understanding of the risk, or an understanding of that obligation to protect, differently than perhaps we've looked at things before.

CHAIRMAN BOTKIN: Thank you, and at this point, I want to move on with our presentations. I'm pleased to see folks are eager to dive into the substance of the conversation, but I want to pick up on some of these important points with the specific questions that have been posed for us a little bit later.

So our next presenter is Cynthia Kelley who's going to speak to us about regulatory mechanisms to facilitate development and approval/licensure of medical countermeasures. Cynthia Kelley came to the Center for Biologics Evaluation Research in 1995, and since 2004, is a senior advisor for Counterterrorism/Medical Countermeasures in the Office of the Director where she is responsible for policy formation and planning, coordinating and implementing activities related to Medical Countermeasures, Receivers, Counterterrorism Program.

DR. KELLEY: Thank you.

CHAIRMAN BOTKIN: Welcome.

REGULATORY MECHANISMS TO FACILITATE DEVELOPMENT AND APPROVAL/LICENSURE OF MEDICAL COUNTERMEASURES

DR. KELLEY: Good morning. So my job is really to explain the regulatory mechanisms we have available to us in FDA to facilitate the development and availability of medical countermeasures in an emergency. And first off, I'd like to start off by clarifying what are the different products regulated by the Center for Drugs Evaluation and Research in the Center for Biologics Evaluation and Research. So the biological products regulated by CBER include blood, blood components and derivatives, vaccines, both preventative and therapeutic, allergenics, cell and gene therapies, tissues, xenotransplantation, and related devices. The drug products regulated by the Center for Drugs Evaluation and Research include what we all think of as drugs, both prescription and generic, and over the counter. CDER also regulates therapeutic biological products that include monoclonal antibodies, proteins intended for therapeutic use, immunomodulators, growth factors, and cytokines.

So the public health challenges of the last decade or so have created a need to change the way we do business at FDA. We have been granting as many pre-pre-IND and pre-IND meetings as a sponsor needs to facilitate product development, and thus this has led to increased collaboration between both the

sponsors, other government agencies, and the FDA. We perform inspections or site visits as needed earlier in the review process in order to help facilitate development of a product. However, we are still charged with paying close attention to the risk-benefit and risk management issues associated with the development and use of medical countermeasures.

In addition, FDA conducts research that's aimed at modernizing our approaches. Examples include developing and evaluating more rapid potency and other lot release and product characterization essays and working on enhanced methods to measure the immune response.

So, as I mentioned, we have earlier and more frequent communication with sponsors of potential medical countermeasures. To advance the availability of medical countermeasures and develop during an emergency, we have worked with sponsors, including the CDC and DoD, to gather data to allow possible use of unapproved products in a declared emergency under an emergency use authorization. To accelerate products towards licensure, we have granted fast-track priority review and accelerated approval processes. In addition, we are working with other agencies and sponsors to develop animal models addressing such issues as dose and route of administration to allow approval under the Animal Rule.

We have found that early and frequent consultation with developers of medical countermeasures improves the quality of laboratory and clinical studies, reduces misunderstandings in the likelihood of multiple review cycles, and improves the efficiency of product development. However, this is a very resource-intensive process. In CBER we have established specific teams that review medical countermeasures.

Prior to the enactment of Project Bioshield giving us the emergency use authorization that would allow the use of investigational products in a declared emergency, FDA facilitated the implementation of protocols for several potential medical countermeasures under IND. In CBER, we called these contingency use protocols. However, use under an IND in an emergency has the potential to be quite cumbersome when there is a widespread emergency because they still require informed consent. Should there be a lab accident or a single case of an infectious disease, such as the couple of cases we've had over the last few years of development of anthrax disease, then use of any unapproved medical countermeasure would be under a single emergency IND for that patient, and emergency use authorization is not available in this situation because there wouldn't be a declared emergency. Emergency use authorization provision has requirements that must be met in order to authorize use of unapproved products or approved products for unapproved use.

And it's important to note that EUA is not a regulatory mechanism, but rather a statutory provision.

So the emergency use authorization was given to us through Project Bioshield which was signed into law in 2004. Under Bioshield, the Secretary of Defense, or the Secretary of Homeland Security, or the Secretary of Health and Human Services must determine that an emergency or potential for one exists. Following such a determination, then the Secretary of HHS can declare an emergency, which could allow use of products under an emergency use authorization. Up to the passage of the Pandemic and All Hazards Preparedness Reauthorization Act of 2013, in March of this year, FDA could not preauthorize use of products. However, now we have a clearer authority to allow us to issue an EUA before an actual emergency event. However, justifying the use of investigational products depends on the circumstances of the emergency or the potential CBRN threat, and the emergency must be due to a chemical, biological, radiological, or nuclear agent. Authorization to use such products under an emergency use authorization are time-limited. They are, in general, for one year, or until the termination of either the declaration of revocation of the authorization.

FDA can authorize the use of an unapproved product or an unapproved use of an approved product if the emergency is declared due to a CBRN agent that can cause a serious or life-

threatening disease or condition, and in which there is no adequate available approved alternative. There must be enough evidence to believe that the product may be effective and that its known and potential benefits outweigh its known and potential risks. There are conditions on authorization of an emergency use authorization. Although there is not informed consent, fact sheets are required both for health care workers and the recipients of the product. These fact sheets must tell health care workers and recipients that this product's been authorized for emergency use, the significant known and potential risk and benefits and the extent to which they are unknown, whether or not there are any available approved alternatives, and because given the option to accept or refuse the product.

Additional conditions on use of the product related to authorization may include the requirement to monitor and report adverse events, recordkeeping regarding who the product was administered to, and reporting that use to the FDA. The use and distribution of a product may be limited by the FDA to a specific population. And there can be conditions imposed by FDA on who is responsible for the collection and analysis of information.

There are several regulatory mechanisms available to speed up potential medical countermeasures through the

development process towards approval or licensure. Fastrack is a mechanism that is typically requested by sponsors during the IND stage of development and applies to the development program for a specific indication. It is designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or a life-threatening condition and demonstrate the potential to address an unmet medical need. Fastrack granted during the IND phase of development can then allow for a rolling BLA or NDA, which means that we accept and start reviewing completed sections of an application for approval or licensure prior to the entire application being submitted and the review clock on that application though starts when the last of the application has been completed.

Priority review is requested at the sponsor at the time of the BLA or NDA submission or just prior to. If granted, then the complete application is reviewed in six months. A product is eligible if it provides treatment where no adequate therapy exists or if it provides significant improvement in the safety or effectiveness of treatment, diagnosis, or prevention of serious or life-threatening disease for biologics, and if it provides a significant improvement compared to marketed products in the treatment diagnosis or prevention of disease for drugs.

For accelerated approval as found in 21 CFR 314.510 or 601.40, a product is eligible if it provides a meaningful

therapeutic benefit over existing treatments for serious or life-threatening illness. Approval is based on surrogate endpoints that are reasonably likely to predict clinical benefit of the product. Post-licensure or post-approval studies are required as part of accelerated approval to demonstrate the effects on outcomes. There can be restrictions as part of the accelerated approval on the use and distribution. We have found in the past that there have been potential problems obtaining controlled data, so then the approval can be withdrawn if agreements are violated or it's not found to be safe and effective.

The Animal Rule as found in 601.90 Subpart H for biologics and 21 CFR 314 Subpart I for drugs provides a regulatory mechanism to approve drugs and license biologics when human studies are not ethical or feasible. The Animal Rule is not a simplified or expedited route to develop products compared to traditional product development. It is not a shortcut leading to faster approval. The Animal Rule cannot be applied when approval can be based on efficacy standards found anywhere else in FDA regulations.

The Animal Rule can be applied to human drugs and biologics, not devices or diagnostics that are intended to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical,

biological, radiological, and nuclear devices. And it's been determined that use of animal efficacy data is scientifically appropriate. Under the Animal Rule, human safety data still needs to be collected. Therefore, requirements on using the Animal Rule, there is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans unless the effects demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. And the animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or the prevention of major morbidity.

Finally, the data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans. The Animal Rule does not address the safety evaluation which still must be demonstrated in humans. Also, the pharmacokinetics and immunogenicity data are needed from humans. Approval under the Animal Rule is subject to post-marketing studies. FDA may impose restrictions on the use of products approved under the Animal Rule.

In addition, the Animal Rule has its limitations. There may be no valid animal model of disease, it can be very difficult to bridge animal data to humans, and the general confidence in products that have been approved under the Animal Rule. However, FDA has been and will continue to be very proactive in working with our federal partners and sponsors developing animal models. We have held numerous workshops on the topic.

The risk-benefit of each potential medical countermeasure differs and FDA must assess each for the product in its potential use. If a product is indicated to treat an otherwise untreatable, serious illness, then it is reasonable to tolerate some risk and some uncertainty. However, if a product is to be used as a prophylactics and given to healthy individuals, either pre or post an event, we have much less ability to tolerate any risk or uncertainty. All products need a transparent, balanced, and effective risk communication and that can be quite challenging in emergency situations.

So in summary, FDA has been proactively facilitating development, licensure, and approval and availability of new countermeasures. As all the medical countermeasures we develop to protect us from potential terrorist attacks or emerging infectious disease, need to adhere to the same standards and principles of other medical products. However, unfortunately

bioterrorism and emerging infectious diseases are not predictable events. It is important that the FDA is looked upon as protecting and reassuring the public and preserving our confidence in medical products and the public health leadership. Thanks.

CHAIRMAN BOTKIN: Thank you.

DR. KELLEY: Any questions?

CHAIRMAN BOTKIN: Norman, I want to remind folks to identify themselves when they ask a question or make a comment.

DR. FOST: Norm Fost. I just want to make sure I understand the big picture here. It sounds like this statute is it? Or regulation? It provides a bypass for the whole regulatory process of approving drugs.

DR. KELLEY: No. It's not a bypass. It helps us facilitate making products available. So the emergency use authorization, once there's been a declaration of an emergency, the FDA can authorize the use of products, but there are still requirements that must be met. So we have to have some data to let us believe that the product may be effective. We also have to have some safety information so that we can assess that the product's known and potential benefits outweigh its known and potential risk. We can only authorize use of an unapproved product or an approved product for an unapproved use if there are no available approved alternative products.

We do still in an emergency always have the option of using a product under an investigational new drug protocol. However, those still require informed consent and emergency use authorization does not. But if you don't have the data that FDA can support authorizing use of a product in an emergency under the emergency use authorization provision, then we still have the option of use under an investigational new drug.

DR. FOST: Right. So if all those criteria are met, then it's not necessary to do specific testing on children under the rules that we're familiar with.

DR. KELLEY: So for an example with the anthrax vaccine that's been debated and discussed so many times lately, the current anthrax vaccine that we have is approved as your typical vaccination to prevent disease. In an emergency, though, the intention of the USG, the U.S. Government, is to use it as part of a post-exposure prophylaxis, not only the antibiotics, but three doses of the vaccine also. We feel confident in this licensed product that we would allow use of this approved product for an unapproved use in an emergency situation in adults 18 and older under an emergency use authorization. However, we don't feel that we have the data to allow use of that product in children, so persons under 17 years of age in an emergency under that emergency use authorization because we have no data in children.

The FDA and CDC has worked very hard. We've also worked with DoD, and we have in place pre-emergency use authorization submissions to allow use of the Anthrax vaccine in persons 17 years and under in an emergency along with the licensed antibiotics. But that would be under IND with informed consent.

CHAIRMAN BOTKIN: So this is Jeff Botkin, and sort of two quick questions. Does the emergency use authorization have any specific language relevant to children?

DR. KELLEY: No.

CHAIRMAN BOTKIN: And then can you also remind us of the role of the IRB in oversight for research that would be conducted in this context?

DR. KELLEY: Of research under using a product under an emergency use authorization? There is no involvement of an IRB.

CHAIRMAN BOTKIN: Steven?

DR. JOFFE: Steve Joffe. For an unapproved use of an approved product, let's say a product that's approved for use in adults, not approved for use in children, but there's an emergency where there's a sense that the product may be beneficial or may be needed for use in children, is there anything to prevent physicians from prescribing that product or using that product in an off-label context? I understand that

that's not necessarily an FDA-endorsed or FDA-licensed use of the product, but is there anything to prevent physicians from simply prescribing something off-label, which is, as everybody knows in the room, common practice in pediatrics anyway?

DR. KELLEY: No, except in an emergency situation, the use of products is covered to cover all liability issues under the Prep Act. And so if you are using a product, and let's say it's supposed to be used under an EUA only in this population. So persons 18 to 65, it can be used under an emergency use authorization, but you need to get informed consent for persons older or younger because it needs to be used under an IND. No, the FDA doesn't regulate the practice of medicine, but there could be issues with coverage for liability under the Prep Act in an emergency.

DR. NELSON: Steve, just to make a quick comment, this is Skip Nelson, on that because I had those same sets of questions as I got into this area.

But part of the difficulty is in an emergency there are many other personnel who would be involved in the administration of these products that are not covered by your discretion as a licensed professional, as a physician. If the product shows up and is released from the stockpile, you as a clinician licensed to practice medicine could use it in any way you see fit. But in the actual distribution of these products

in an emergency, many of the personnel who would be distributed are not covered by that, and so there needs to be a much more structured context within which they're covered to be able to administer these products.

CHAIRMAN BOTKIN: And this is a lot of new and important information. I'm going to let this conversation go for a little longer, Dr. Bradley and Dr. Daum.

DR. BRADLEY: John Bradley. I'm particularly interested in working with the FDA. Cynthia and I had many conversations over many meetings. But Dr. Fost's question about the difference between getting a drug in an EUA situation and in IND situation is actually quite different. And although the FDA is trying to streamline the IND situation, I think the differences are still very important. As she mentions, if there's some preliminary data, whether it's radiologic toxin, bio-terror, if there's some preliminary data on safety, then the FDA will allow the EUA a mechanism which doesn't require informed consent. So if Steve's got thousands of kids lining up in his ED in Chicago, he can give the drug without having to get informed consent from the parents.

On the other hand, if it's an IND, currently, for regular vaccines, they're 24, 25 pages long, and the whole process takes an hour or so, and that's just impossible an event. But Cynthia and her crew are streamlining that so that

for an IND in one of these bio-terror situations it would be quicker, but it still would take longer than EUA. And so I just wanted to compare, and I would like her to correct anything that I say.

DR. KELLEY: No, we have worked very hard with DoD and mostly CDC, and when Sue speaks, she can elaborate a little bit more. But, for instance, the current informed consent to give AVA, for example, in a declared emergency to persons 17 and under, under IND is two pages long. So I know all of you doctors are much more used to what John says, the very thick ones take a long time to go through the informed consent. But we have really streamlined the informed consent because the point here is to administer the vaccine. We are not conducting a research study. What data can be collected in an emergency, that's all grand and would help us, we hope, but again, it's not controlled like the data FDA wants to approve something for a particular population or indication, et cetera. The idea is get the product to the people as fast as possible.

CHAIRMAN BOTKIN: Dr. Daum, did you have something you wanted to jump in on?

DR. NELSON: Well, I see Leonard over there with a furrowed brow, so I just wanted to make a comment that might answer his question. An EUA is not research. So the emergency use authorization is not research. So, effectively, you do get

informed consent. I mean, you don't stick needles in people without asking them, "Can I stick a needle in you?" But it's not different than the informed consent you would get clinically to deliver any other vaccine. There's an information sheet that's distributed, et cetera. The important difference is you don't need a signed document of informed consent to go through that step, if you will, that is important for IND research. It's not that the EUA doesn't require the consent of the individual receiving that vaccine or that they don't get any information, but it's in a clinical framework not a research framework.

CHAIRMAN BOTKIN: I have Dr. Daum, and then we're going to have to wrap it up pretty quickly.

DR. DAUM: So I'm trying to get my arms around what's being said here. And I've always been a sort of a lay FDA advocate and not ever a member of the FDA per se. But I've always said that FDA approves things when they are safe and effective, and that's the holy mantra, safe and effective, safe and effective. So what I'm hearing this morning is that safe and effective asterisk, except when there's an emergency use authorization, and what I'm hearing is that you'll make that as safe and effective as possible, but there's no language in there that speaks about research agendas or particularly about administering things that aren't safe and effective but

authorized under an emergency use to children. So I just want to clarify. It seems to me that Skip and others have said the agenda is we're talking about research approvability and you're talking about FDA's emergency use authorization that may or may not apply to children, and they're not necessarily the same thing.

DR. KELLEY: So with the emergency use authorization, we, the FDA, to authorize use of a product, have to have enough data to determine that it may be effective and that the known or potential benefits outweigh the known and potential risk. That requires data. So what we have done for the last several years is we have in place what we call pre-EUA submissions. So we, FDA, the regulatory review team on a particular product, determines the amount of data, that is safety data and efficacy data, whether the efficacy data is in animals or not, and the amount of safety data, which usually, thus far, has been adults.

So we determined, even though anthrax vaccine is not approved for a post-exposure prophylaxis situation, that we had enough safety data through its approved use and efficacy data in animals in a post-exposure prophylaxis situation with licensed antibiotics, to determine we could allow adults to be given that product in an emergency under an EUA. But we have determined that we do not have enough data; in fact, we have no safety data in children at all. And so we've determined that it has to be

used under an IND in children until, if and when, we had some data in children. And that likely would occur in an emergency situation where children were being given the AVA under an IND, for instance, then perhaps we would be lucky enough that we collect some safety information on the use of that product in children.

And the IND that is set up with CDC to administer this product in an emergency to children has provisions in it for attempting to collect safety data on children to the best of our ability, knowing that, depending on the size of an emergency or whether or not it occurred, the chaotic situation might not allow the collection of too much information, but we have it set that we will attempt to collect that information. That information collected in the event it was used under an IND in an emergency in children, then could maybe be used by us to inform a future event allowing its use under the EUA in children.

CHAIRMAN BOTKIN: Dr. Glantz.

DR. GLANTZ: I just had a question for Skip. By the way, I thought that it was an important point that the requirement for informed consent doesn't just come from the FDA, that there are other places where that requirement comes from if you were going to give an unapproved vaccine to citizens, to kids. You mentioned that in response to Steve's question about

physicians being able to use anything that they can get their hands on essentially to treat patients, you said that covers physicians but not other people who have to handle it, if I heard you correctly. Pardon me?

DR. NELSON: Well, that will depend on state law. And I think that's part of the complexity. This is not my area, but I'm sure others could speak to it, but when it indicates a national emergency when the truck shows up with the stuff that's going to be used by the clinicians, that will be distributed often by people that are and other covered under physician licensing, or may or may not be covered under nurse licensing or physician assistant licensing, so on and so forth. So it's state-by-state what those licensing laws are. So my only point was to Steve. As a physician, per se, he's not limited in the use of those products in any way he sees is appropriate for the care of his patients, not that no one else necessarily is because that's not my area of knowledge.

And if I could just make one point to Bob's earlier. To give an example of an EUA that might be a little closer to home or more understandable, oseltamivir during H1N1. In other words, there's data to support the use of that. That was given to children under an EUA because it hadn't reached the level of data to label it as safe and effective to be on the market to be

used by anybody. But during the H1N1 pandemic, it was released under an emergency use authorization.

So the FDA has a lot of mechanisms. This is not the only one. Humanitarian use devices in the device book is considered one. There's other accelerated approval. There's a lot of mechanisms for single patient INDs, and so on and so forth, where the FDA has flexibility in allowing the release of a product that does not yet meet the bar of licensed as safe and effective because of the understanding of the risk-benefit may be different in individual circumstances.

DR. DAUM: And that was my central point, is that EUA changes the game and things can be released that haven't gone through these minimal risk and things that we're so carefully discussing today.

DR. NELSON: Right, because you have a declared emergency.

CHAIRMAN BOTKIN: Okay, Dr. Wilfond.

DR. WILFOND: My question was actually --

CHAIRMAN BOTKIN: This goes back to John's point at the beginning.

DR. WILFOND: Actually, Jeff, my question was already answered.

CHAIRMAN BOTKIN: Norm, you have some questions?

DR. FOST: Just a very quick one. Skip, when you say these other health care personnel are not covered, not covered for what? For malpractice laws?

DR. NELSON: Again, I'm not a lawyer. I don't play one on TV.

DR. FOST: But what did you mean when you said not covered?

DR. NELSON: The various personnel when you are in an emergency that are distributing these products to people that are lined up in a long line, given the emergency, may or may not be covered under their state licensure procedures for the administration of that product. That's all, because it's not just physicians that are lining up because you've got long lines of people in an emergency. So --

DR. FOST: But that would be true of all off-label prescribing. It involves nurses and other personnel.

DR. NELSON: Depending on the state. They may or may not be covered. But they might not be using nurses. I don't think we need to get off on that point. It's very tangential to what we're discussing, but it is state by state, which is why you have this general federal coverage.

CHAIRMAN BOTKIN: Dr. Roberts.

DR. ROBERTS: For an example, when medicine is being distributed at a point of distribution, there are no

prescriptions being given to the patient. So a physician could go ahead and give it under a prescription, but the nurses, or just whoever it is that's handing that out is doing it under the Federal Emergency Use Authorization. That's all part of that.

CHAIRMAN BOTKIN: Okay, the last two comments, then. Dr. Krug?

DR. KRUG: Yes, just a wayward example of the point they made. I mean, this could be delivered by a postal worker to your home. And the postal worker, essentially, is going to follow the state rules and regulations and does not have the ability to give something that is not specifically approved. That has to happen at a place where a clinician who has the right to do that can do that, which then creates a barrier for access for special populations, as an example, in terms of whether they get a drug or not.

CHAIRMAN BOTKIN: Dr. Joffe.

DR. JOFFE: Steve Joffe. Since we're talking about mechanisms, and one of the main challenges or problems with requiring an IND for use of a product for which there's not enough information to use it under an EUA or a licensed fashion, is the time and concern about, is it feasible in a mass public health emergency to go through the important consent requirements that would ordinarily be true of IND research? Has there been any consideration at the FDA to conceptually

extending the emergency exception to the informed consent requirements that we typically think of as being applicable, for example, in research on after cardiac pulmonary arrest, where someone who might otherwise have the capability to consent is just not feasible in this context, or they lack the capability in this moment, and there's no time to look for a proxy, et cetera. Conceptually, to be extending that to the situation of a public health emergency, where, although, if we had more time, that people involved would have the ability to give informed consent or a proxy permission, but in the context of this public health emergency, it's not realistic, not feasible to think of going through informed consent one by one by one.

OPERATOR: -- is now joining.

DR. ROBERTS: Rosemary Roberts. I'm not sure how that would really help the situation. It would seem to me that you would really be doing more of an emergency use authorization, except that you would try in retrospect to get somebody to sign once there was time to do it. And are you referring to emergency use and under a specialized IND where the individuals do not have time to give informed consent? Are you referring to that process?

DR. JOFFE: I'm referring to the sort of process whereby, if we were talking about a new drug given to people in the context of cardio-pulmonary resuscitation, that there's

reason to think that it might improve outcomes after CPR. One can never study that drug if one required informed consent for the experimental use of that drug. And so I'm conceptually taking that mechanism and wondering if it has any relevance to the situations that we're talking about, where, in the context of a mass public health emergency, one has to get through a very large number of people very quickly, but one still wants to do rigorous research.

So I'm thinking about a protocol where we have waived the requirement, or made an exception to the requirement for informed consent, because in the context of the kinds of situations we're talking about, we all agree that it's not feasible to get individual informed consent or individual parental permission. It doesn't preclude us from giving out information sheets and make all the information available, but it does mean that we don't have to walk through those step by step by step for half an hour, and it does mean that we don't require a signature. That's the proposal, and it doesn't solve all of the problems that we're talking about. We would still like to have more data when we go to use those drugs in children in the event of a mass emergency. But it could at least help with part of the problem.

CHAIRMAN BOTKIN: Skip.

DR. NELSON: It does take us a little bit off topic, but I'll respond to the topic. My own view is that the reason we think that informed consent might not be feasible in this circumstance is because of the somewhat onerous standard we seemed to have developed in the research circumstance where it's a 18-page form that most people can't understand. Imagine you've got a pod where people are lining up to get their antibiotics because they've been exposed, and it's going to take 20 or 30 minutes to get through that line, maybe longer. If you've ever been to Disney World, you're actually pretty well-informed about everything else that's at Disney World by the time you get to the end of that line, because you've got videos, you've got all other kinds of things. It's nothing to say you can't bring everybody into an auditorium and deliver one speech to everybody and then have them sign a piece of paper as they walk out.

So we have this, somehow, this conception of what the normal is for informed consent. I think that's the problem, not that it's not feasible in this circumstance. And that would take us off on a bit of a tangent. But, I guess what I'm saying is that I don't necessarily accept your premise that it's not feasible in this circumstance. It's operationally more difficult than the EUA, and that's part of the reason this whole

discussion is happening, because of the concern about that operational difficult.

CHAIRMAN BOTKIN: All right, I'm going to move on, but thanks to everybody for that conversation, and Ms. Kelley for her presentation. Our next speaker is John Alexander, speaking about Pediatric Labeling and Medical Counter-measures: Anthrax Examples. Dr. Alexander is a pediatrician who completed a joint FDA Children's National Medical Center Fellowship in pediatric infectious diseases. Dr. Alexander has worked as a medical officer at the FDA for more than 15 years; currently a Medical Team Leader in the Division of the Anti-Infective Products in CDER. Dr. Alexander, welcome.

PEDIATRIC LABELING OF MEDICAL COUNTERMEASURES:

ANTHRAX EXAMPLES

DR. ALEXANDER: Good morning. So, what I'm going to try and do is go through some specific anthrax examples of products that we actually have labeled and approved as medical counter-measures for anthrax. But what I'm going to start out by doing is talking a little bit about the background that we have with regard to traditional NDAs and how we go about with approval and labeling for those products. And I'm hoping that the contrasts between what we do with traditional NDA approvals and what we've done with the examples of the medical countermeasures will be somewhat informative.

So, with regards to traditional NDAs, the standard for approval is to have substantial evidence of effectiveness that come from adequate and well-controlled clinical trials, and there are regulations that describe the characteristics of what we'd consider adequate and well-controlled trials. So, on that basis, when we are looking at approval of new products, you basically have to have conditions that are usually fairly common in order to be able to have adequate numbers of individuals to be able to study and to be able to evaluate the effectiveness of a drug that's used in a population.

Now, the requirement for substantial evidence of effectiveness, I think the word "substantial" is one of the keys

there, that it doesn't have to be an overwhelming preponderance of the evidence; there just has to be some evidence with regards to the efficacy. And I think it's important that the regulations cite that there is scientific judgment that's applied in determining what amount of data are needed for determining the effectiveness for each particular drug, because each situation is different.

So, what we end up doing when looking at the approval of traditional NDAs and the supplies to biologics as well, because there are analogous regulations for biological products, but what we end up doing is basically making a benefit-risk assessment. When we're doing that benefit-risk assessment, what we have is the evidence of benefit that's demonstrated within these adequate and well-controlled trials, and we're usually looking at the known or potential risks that those known risks may come from the data that is developed in the adequate and well-controlled trials. So, you're looking at the direct comparison of efficacy versus safety within a phase three trial or a set of phase three trials that are done for a particular product in a particular indication. Or those known and potential risks may also come from what's known about the drug, what's known about the particular class, what's known about the drug from other uses as well. But a lot of the focus is actually, when we're looking at traditional NDA approval, is on

efficacy that's coming from a set of phase three trials and also the data on safety that provides you the most direct comparison.

Now, it is important to point out that these trials are typically conducted in adults. There are always the exceptions that come about when there are conditions that are specifically conditions in children, but not conditions that occur in adults, but as I said, typically what we're dealing with are products that have adequate and well-controlled trials that are conducted in adults.

So, then, we get to the issue for traditional NDAs with regard to how do to label for pediatrics. And so what we're able to do in some circumstances is apply what's called pediatric extrapolation. This is actually the statuary language that describes that effectiveness can be extrapolated from adequate and well-controlled studies that are conducted in adults, usually supplemented with other information that's obtained in pediatric patients; so, that other information typically being information on the PK and safety of drug used in the same indication that would be applied to adults.

We're allowed to extrapolate pediatric effectiveness in certain situations and the Division of Anti-Infective Products, where a lot of these products for anthrax are regulated, has actually used extrapolation for labeling of antibacterial drugs fairly commonly. So we've applied it for

pneumonia. We've applied it for skin infections. We've applied it for HIV. There are, again, exceptions where an unusual circumstance, like for otitis media, for example, you can't necessarily apply extrapolation because the fact that the disease, the condition itself, is different from what occurs in adults, but for antibacterial drugs in general, it's usually fairly easy to apply an extrapolation of the condition because the condition is similar in what we expect the effects of the treatment on usually killing the bacteria are going to be fairly similar between adults and the pediatric patients. So that the additional data that we get on safety and PK are sufficient to allow us to make those types of extrapolations.

Now, again, the issue here, though, is that we're usually dealing with conditions that are fairly common in both the adult and the pediatric population. When we're sort of applying this extrapolation, we actually know a lot about the condition itself.

So at this point I think it's important to talk about anthrax as a disease. As an infectious disease person, of course, I have to describe the condition that we're talking about. So, anthrax is caused by the bacterium bacillus anthracis. It's a spore-forming gram-positive rod. The reason that we are so concerned about this is the disease process involves inhalation of spores, and we already know that these

spores have been prepared in what are recognized packets that are able to be developed, that are able to be delivered by inhalation. These spores germinate in the lung and then bacteria multiply. It's not the same sort of condition in as other infections where we think about where the multiplication, the bacteria are spread to different sites are the problem. The issue with anthrax, a lot of it is related to the development of particular toxins that the bacillus anthracis produce, particularly edema toxin and lethal toxin. The toxin production actually involves a particular antigen that's called protective antigen and that'll play in a little later.

So, inhalational anthrax as a disease was something that was historically recognized as Woolsorter's Disease, and there are also gastrointestinal and cutaneous forms, but again, we're not talking about a disease or a condition, even with the cutaneous forms, that are common enough for us to be able to study in humans and do the types of adequate well-controlled trials that are necessary to approve a product for this use. It is a very rare condition in humans.

Antibacterial drug labeling for anthrax: We do have several products that are labeled specifically for inhalational anthrax post exposure that include procaine penicillin, doxycycline, ciprofloxacin, and levofloxacin. The approval of these are actually the evidence that comes for approval for the

benefits, actually comes from animal models. So, there are animal studies that have been conducted that showed reduced mortality with antibacterial treatment in rhesus macaques that actually the evidence of the benefit of the drug. Now, this evidence of benefit is applicable to both the adult and pediatric population. So, you heard a little bit about the Animal Rule in Dr. Kelly's presentation, and so the Animal Rule actually talks about extrapolation of, not extrapolation, but it talks about the determination that the benefit is reasonably likely to apply to humans. And so the Animal Rule basically allows us to apply data from animal models to humans when we think that that is reasonable. I actually think of the application of Animal Rule as being somewhat similar to what we do with pediatric extrapolation, where we take data that are generated in adults and apply it to the pediatric population. Well, the Animal Rule is kind of similar, but what we're doing is taking data that comes from animals and we're applying it to humans, both adult humans and to children, if we think that that application is actually something that is meaningful.

So, when we've used the Animal Rule and applied the results of the animal studies, what we also had was PK and safety data for both adult and pediatric patients that comes from the use in other infections. So, this is a little bit different from the description of what goes on with regards to

traditional NDAs where what we're doing is actually taking information on safety and PK that comes from these other uses and making a benefit-risk assessment that takes a look at a different condition than what we do with the adult approval of drugs where we're looking mainly at the direct comparison within a set of clinical trials of the benefits and risks that accrue when you study it for use in a particular population. And for these products, what we have is labeling in the indications and usage section, the dosage and administration section, information on the safety of the product, and information in a pediatric use section that describes how we came to label these products.

So, I'm moving on now to a different example, and this example is different because unlike the other products, doxycycline, ciprofloxacin, where we can have studies of product in other uses, with raxibacumab, what we have is an monoclonal antibody that its mechanism of action is to bind protective antigen and basically prevent the development of toxins. This BLA was approved by the Center for Drugs in December of 2012 under the Animal Rule. The product is approved for treatment of inhalational anthrax in combination with antibacterial drugs. So, the idea would be that you would usually expect that you would be using this for treatment of individuals who actually have anthrax disease and it would be expected to be used in

combination with antibacterial drugs, and it's believed that the combination is likely to further reduce mortality in comparison to the use of the antibacterial alone. So the efficacy of the product is based on animal models. Again, there is evidence of mortality benefit in New Zealand white rabbits and cynomolgus macaques when you use the monoclonal in comparison to a placebo.

The product was also had safety and PK studies that were done in adult volunteers and that was the safety and PK data that we were able to use to take a look at the animal model and judge, again, the overall benefit versus risk assessment to make the determination that the likely benefits exceeded the known and potential risks of the product.

So, raxibacumab for pediatrics, we actually did indicate the product for both adult and pediatric patients. However, I'd point out that we labeled it with a limitation of use, indicating that there were no studies of raxibacumab that were conducted in the pediatric population and that dosing was derived using the population PK approach. So, the PK modeling approach that was used was that there were the adult data for the PK of raxibacumab that was known as well as data that we had for PK in clearance of other monoclonal antibodies data that we had for both adult and pediatric patients for the use of these other monoclonals, and that data was used to then derive what we think is a pediatric dose regimen that models the PK that was

seen in adults. So, it allowed us to determine what we think an appropriate dose would be that would basically give children the same exposure that was seen in adults and that same exposure that was related back to the animal models as the dose of the product that would likely confer the benefit on reducing the production of anthrax toxin.

So, when we decided to label the product for pediatric patients and considering the benefit-risk assessment, what we did is we looked at what we think is the mortality benefit that's been demonstrated though these animal models and we compared that to the potential unknown risks that would occur in the pediatric population because we didn't really have data in children to tell us what the known risks would be. We did have the safety data in adults that we knew about. We do have information that with the other monoclonals that we don't really expect or see real differences in the safety data or the safety of the monoclonal antibodies that we have used in both adult and pediatric patients, but the issue here is what we're weighing against is potential unknown risks. So, there is the potential that the administration of raxibacumab may have some unusual effect in children that hasn't been recognized, but when we're weighing that against the potential benefit on reducing mortality, even if that reduction in mortality may be small, the overall benefits versus risk we felt were outweighed.

So then in summary, for traditional antibacterials, we have often used pediatric extrapolation for antibacterial drugs and for pediatric labeling. Then for these medical countermeasures, there is an applicability of animal model data under the Animal Rule to the pediatric population as well as to the adult population. So, as long as we think that the data that we're generating from animal models will apply to pediatric patients as well as to the adults, then we have that information that provides us the basis for sort of making some determination of benefit.

So, what we then do with traditional antibacterials is oftentimes we can leverage safety and PK data that comes from other uses if that's available to make an overall determination of the benefit and risk. With raxibacumab, we have an example of where we didn't have that data available and yet we still have other modeling approaches, if the data is limited, that we can apply. But that circumstance, that example for raxibacumab, may not apply to all situations.

Thank you.

CHAIRMAN BOTKIN: Thank you. Questions for Dr. Alexander?

DR. GRABENSTEIN: John Grabenstein. With the raxibacumab, did the sponsor make any effort to assess efficacy of pediatric macaque to adult macaque, or kinetics of pediatric

macaque to adult macaque?

DR. ALEXANDER: Not that I recall. No. I think the issue there is that what we did was modeling in animals, and I think that there was variation in the ages of both the cynomolgus macaques as well as some variation in the age of the rabbits, but what we're talking about in those situations where we've been applying it is that there is particular disease process that is occurring. We understand that the spores germinate, the bacteria multiply and are able to sort of produce these toxins that can be harmful, and that process is expected to be the same in animals as well as in adults that might inhale spores or children that may inhale spores. So, we're really looking at sort of the efficacy of the product more so than we're trying to evaluate, well, was it a juvenile animal model or an adult animal model.

DR. BRADLEY: Thank you very much, John. I think this is a success of the FDA in creating a product that has great implications for medical countermeasures and has applicability for individual cases of botulism that come up. And I'm on one of the groups that's trying to put together guidances for botulism in case of a bioterror event. So, there are twelve different doses that have been modeled out for kids as you know, but it's using the animal to extrapolate to humans, of course, is something that you do when you can't really test it. But the

concept of approving a drug is one thing, which you've done with this monoclonal for botulism. Have you ever done studies in animals that will allow you to get an EUA for an event? So, it's not quite getting approval, but it's getting sufficient information so that if there were an event, you could justify an EUA. And I know you're an anti-infectist, but it would apply to, you know, anti-sarin gas, anti-radiation, the whole thing. Thank you.

DR. ALEXANDER: Yeah, I'm not necessarily familiar with EUA examples that we've had in the anti-infectives, but Dr. Kelley?

DR. KELLEY: So, Cynthia Kelley. So, Dr. Bradley, the botulism, are you referring to the heptavalent botulism antitoxin that CBER just approved?

DR. BRADLEY: Yes.

DR. KELLEY: Okay. So, prior to that approval, there was a point along the development of that product where we determined that it had enough data to support its use under EUA in an emergency. So, we had a pre-EUA submission was sent by us by CDC, based on data collected by the sponsor, Cangene, and then we had a pre-EUA in place should there be an event that we needed to use the heptavalent bot antitoxin. And our pre-EUA in that case was for use of the product in persons of all ages. Likewise, when the bot heptavalent antitoxin was approved, we

determined that it could be used under its license in persons of all ages. So, CBER has an anthrax polyclonal immunoglobulin. It's under development by the company, and likewise, at some point along its development pathway, we had told the sponsor in advance how much data we would want to allow that product's use under EUA in an emergency, and we do have a pre-EUA in place for that ready to authorize should we need. And again, because of the ability to extrapolate historically on the use of immunoglobulins and antitoxins, we extend that pre-EUA to persons of all ages, so including pediatric populations.

CHAIRMAN BOTKIN: Dr. Alexander, thank you. Next speaker is Dr. Susan Gorman. Dr. Gorman, I understand, you're on the phone?

DR. GORMAN: I am here. Can you hear me okay?

SNS RESPONSE TO PUBLIC HEALTH EMERGENCY

CHAIRMAN BOTKIN: We can. Thank you. I'm going to give you a quick introduction here. Dr. Gorman is going to be speaking about strategic national stockpile response to a public health emergency. Dr. Gorman is a licensed pharmacist and board-certified clinical toxicologist and serves as the associate director for science for the CDC's division of Strategic National Stockpile, where she provides oversight of the formulary as well as expert pharmaceutical and toxicological advice on issues surrounding stockpiling. She's been with the CDC for 14 years. So, Dr. Gorman, thanks for joining us.

DR. GORMAN: Thank you. I'm going to start on slide two. Well, today's stockpile is more than just a bunch of stuff sitting in warehouses. We do acquire and manage all the medical countermeasures according to the Public Health Emergency Medical Countermeasures Enterprise, which establishes our requirements now for stockpiling for each threat agent, but we also support our federal, state, and local and private sector partners because they're the ones that are going to have to distribute and dispense all these medical countermeasures to the people. So, we want to make sure that they're able to take what we give them and make use of it.

We also support various parts of CDC in creating guidance and policy so that we can do an effective

implementation of response. So, that means supporting scientific research here at CDC, supporting our subject matter experts that are going to provide clinical guidance on how to use the countermeasures, and our regulatory affairs, who are responsible for submitting and creating all those pre-emergency use authorizations packages that Cindy referred to earlier.

We also provide our subject matter expertise in all parts of stockpiling and participate on many workgroups that inform those issues. We help create and manage alternate and surge supply teams. For example, during hurricanes, we can fill in as an alternate supply chain. And we now go out and do an annual review of all the state plans to receive stockpile assets and assign a score to those plans so that we can show continued progress throughout the years.

Slide three, please. So, in order to be able to respond to a public health emergency, we have our inventory configured in a number of different ways; three ways, basically. The first is called managed inventory and this makes up the large majority of our inventory. And that can either be managed by the stockpiler or managed by a vendor, and I'll talk more about each of these examples in just a moment. We also can forward deploy countermeasures to meet clinically relevant timeframes. So, if something needs to be administered within minutes to a half an hour, we wouldn't be able to get it there

through our traditional deployment response. So, we can forward, place those items. Then we also have what we call our 12-hour push packages.

Slide four, please. So, let's start with managed inventory. There are two kinds of managed inventory. Stockpile managed inventory, which is managed by third-party logistics warehouses around the United States that we contract out for. And we put things in stockpile managed inventory when we need a quantity of material that will exceed what's available from the supply chain, or if we need to provide it to a state before a timeframe where we could rapidly purchase it and send it out from the regular supply chain. And this is also effective when a countermeasure is not commercially available. For example, there's not a large market for anthrax vaccine commercially, so that's something that we could put into stockpile managed inventory.

We also have vendor managed inventory, the difference being that these are items that are actually stored with the manufacturer. And we do that when they can actually use what we have that's stockpile owned and rotate it back into the commercial market so that we never have anything expire on the shelf. So there aren't too many items that we have where we have not already exceeded what would normally be used in the United States on an annual basis, but for those items that can

be rotated back into the commercial market, a vendor managed inventory is a possibility.

Slide five. An example of our forward-placed caches would be our chem pack program. As you know, chemical nerve agents have to be administered quickly after an exposure, something that we could not send through our regular stockpile response. So we have what are called chem packs that are placed all over the United States in hospitals, fire stations, EMS stations, et cetera. And they contain chemical nerve agent antidotes that are federally maintained, but locally managed, and so they can enter into those containers and get the nerve agent antidotes without federal permission.

They have integrated these chem packs into their local Hazmat response. They're in little containers that are movable from one location to another. For example, if they need to further forward deploy them during an event, they can do that. They are monitored for temperature remotely. Each chem pack container is identical; however, there are two configurations. The hospital container contains more multidose vials and fewer autoinjectors, and an EMS configuration contains more autoinjectors and fewer multidose vials.

In addition to the federally-managed forward-placed caches, we also do sometimes give away material that can be managed locally. An example of that would be our providing

calcium human zinc DTPA for a potential radiation event, for those countermeasures, would be right there locally if needed.

Slide six, please. We also provide a board spectrum of support through what we call our 12-hour push packages. And these are used to respond when we don't have a clear idea of what kind of threat we're dealing with. They're pre-packed and configured material in transport-ready containers that can go out either by air or by ground. And each push packages weighs 50 tons. This makes up a small portion of the stockpile inventory. We have these prepositioned around the United States in facilities near major transportation hubs so that we can get them anywhere in the United States or our territories within 12 hours or less of the federal decision to deploy. They are delivered rapidly by commercial transport partners. These are by air or by ground. And each push packages is identical to one another. They're color-coded so you can tell at a glance that the container contains oral antibiotics, airway supplies, et cetera.

Slide seven, please. Our formulary was initially developed in 1999, and it was based on threat agents that caused smallpox, anthrax, botulism, viral hemorrhagic fever, plague, and tularemia and also chemical nerve agents. And later on, years after that initial formulary development, radiation countermeasures and tend to make influence and countermeasures

were added to the stockpile.

So, I'm going to focus mainly on the Category A, biological threat agents, chem, and radiation.

Next slide. Slide eight, please. I do want to point out that everything we have in this stockpile for adults, we have also taken children into consideration as well. I want to just start with anthrax and just give you some examples of what we have in the stockpile for anthrax. We do have the oral solid antimicrobials and the liquid formulations of antimicrobials. And these are FDA approved for pediatrics. An example here would be ciprofloxacin, tablets and suspension, used for post exposure prophylaxis in anthrax. And it's FDA approved for all ages.

We do also have a selection of IV antimicrobials in the stockpile and some of these are FDA approved for pediatrics. Again, an example would be IV ciprofloxacin. However, we do have antimicrobials that are not FDA approved for post exposure prophylaxis or treatment of anthrax for any age, and therefore would require youth center emergency authorization. And examples here would be amoxicillin for post-exposure prophylaxis and vancomycin for treatment of anthrax.

We also have anthrax vaccine, as was earlier mentioned. And this would need to be used under an emergency use authorization for ages 18 and up, and under an

investigational new drug protocol for age 17 and under. And as you know, anthrax vaccine is an FDA approved drug, but it's not FDA approved for post exposure prophylaxis of anthrax.

And then we have the two antitoxins that were mentioned earlier. One is currently FDA approved for adults and pediatric patients with no age restriction. And the other is not FDA approved yet for any age but can be used under an IND or an EUA with the proposed use for all ages.

Slide nine. For plague and tularemia, again, we do have the different types of antimicrobials in the stockpile. We have the oral, solid, and liquid antimicrobials which are FDA approved for pediatrics. An example here would be doxycycline. However for plague and tularemia there are age restrictions on doxycycline, and it is not approved for use in children eight and under. And also, doxycycline tablets and liquid are approved for treatment of plague and tularemia, but not post-exposure prophylaxis, so that would require an EUA or IND.

We also have the IV antimicrobials which are approved for pediatrics, but may not be FDA approved for plague and tularemia, and therefore would require an IND or an EUA. And an example here would be gentamicin.

Slide 10, please. For botulism our two mainstays are botulism antitoxin heptavalent, a product that was recently FDA

approved, and this is FDA approved for all ages, and we have ventilators that are approved for use down to 5 mg.

Slide 11, please. For smallpox we have multiple types of vaccines; three types currently. One is currently FDA approved for all ages. The other two are not yet FDA approved and must be used under an emergency use authorization for all ages.

We have vaccinia immune globulin to treat the side effects of the smallpox vaccine, certain side effects, and that is FDA approved for all ages. And we currently have one antiviral that is not yet FDA approved for the treatment of smallpox, and it requires an IND or an EUA, which includes proposed dosing for all ages.

Slide 12, please. For chemical we do have the chemical nerve agents that are forward deployed in the chem packs all over the United States. The atropine and pralidoxime are FDA approved for pediatrics, and the diazepam is approved but has some age restrictions and is not approved for neonates less than 30 days of age.

For radiation we have oral chelators such as Prussian blue, which is FDA approved for pediatrics down to age 2. Under age 2 would require an emergency use authorization. We also have I.V. chelators such as calcium and zinc DTPA. For example, zinc DTPA is approved for all ages, but all dosing routes that

are approved for adults are not approved for children, and the nebulized route is not approved for children.

And we have some anapolytic agents. An example here would be Neupogin. It is an FDA approved drug, but it is not approved for treatment of acute radiation syndrome and therefore would require an IND or EUA for all ages.

Slide 13, please. So how would SNS respond? The majority of the work for how we would respond has taken place under the Cities Readiness Initiative, which is a federally-funded initiative that prepares all major U.S. cities to effectively respond to a large-scale bioterrorism event. And the scenario that the Cities Readiness Initiative works under is an inhalation anthrax event. And the work is mainly towards dispensing antimicrobials and other medical supplies to the entire identified population within 48 hours of exposure.

Slide 14, please. And the way that this is going to occur was mentioned earlier, and it’s through points of dispensing. So basically what happens is the Strategic National Stockpile will send out supplies to a pre-designated location, and the material is further dispensed or pushed out to these points of dispensing. And the traditional point of dispensing is where people are pulled into a location. So these might be set up in places like school auditoriums, large places where there is plenty of in and out availability, places to park, et

cetera. And people are pulled in to get their post-exposure prophylaxis.

But there are other ways that this is going to be accomplished as well, because everyone is not going to be able to get to one of these points of dispensing, so it was previously mentioned there's a postal plan where postal workers can actually deliver medications to the homes. There is something called a home antibiotic kit that is currently under discussion that could be pre-positioned in people's homes. There are pre-deployed community caches for large captive population, for example, prisons, nursing homes, etc. They may have their own post-exposure prophylaxis supplies on hand so they can just dispense those to the populations right there. And there's also consideration of pre-event dispensing to first responders so that they can actually respond during an event.

Slide 15, please. So what happens is once those theaters or city becomes overwhelmed and can't respond on their own anymore, a request can be made for assets from the Strategic National Stockpile. And a difference here in requesting SNS assets is that a presidential disaster declaration does not have to be in effect and the national response framework does not need to be activated in order for us to send out assets.

We already know where we're going to send all the assets out to every state and territory. We have pre-designated

receive store stage areas to which we're going to send the supplies that have been chosen by the states. And then the state and city further distributes the medical countermeasures to their pre-designated points of dispensing or other locations such as hospitals.

The stockpile can also send out directly to hospitals those medical countermeasures that are not going to require a point of dispensing.

Then the points of dispensing are open and staffed locally. There are different kinds, as I mentioned. There are the open points of dispensing where anyone can go there and pick up their medical countermeasures. There are also things called closed points of dispensing, and the CDC has been working hard trying to get businesses and other large entities on board with becoming closed pods. Examples would be the CDC providing prophylaxis for all of its own employees and family members. Places like the IRS have done that, IBM, so large businesses that have a lot of employees are being solicited to become closed pods for their own employees and families.

There's also the nonmedical versus the medical model that was alluded to earlier. If you have millions of people that are going to require post-exposure prophylaxis, not all of them are going to get it from a physician or a licensed healthcare professional. There may be volunteers that are

working under the auspices of a healthcare professional handing out these countermeasures, and they are not necessarily going to be asked a large amount of questions; maybe a few questions as to whether or not they have an allergy or serious medical interaction with another drug they might be taking. But not everyone is going to get a large medical exam before countermeasures are handed out.

And use of the medical countermeasures under an IND or EUA is going to require some additional paperwork. Informational materials need to be handed out about the risks and benefits of the drug. If it's IND, it's going to be written informed consent; if it's EUA, it just has to be informed.

Next slide, please. Slide 16. So there are a lot of challenges as you can imagine with responding to in an event like this: the timeframe that we have to respond to for effective prophylaxis, everyone getting pills within 48 hours of exposure, and the amount of staff that are required to staff up these points of dispensing which can be upwards of 5,000 volunteers to provide prophylaxis to a million people. Those are very challenging things to meet.

Also there's a lot of local staff turnover and repeated training that's required for everyone at the local health department level. A lot of staff turnover, then you have to train someone else up about what are these points of

dispensing and how is that going to work. As you all know, there's declining funding and eroding public health infrastructure, and preparing for a terrorism event is not always highest on the list of things that need to be done on a daily basis.

We have the United States Postal Service model that I alluded to earlier. Part of the problem with that is that there is no patient screening. It's a nonmedical model. And also the postal workers would like to have security along with them when they're delivering the medical countermeasures. There is not enough security to provide someone for every postal worker.

There is difficulty with crushing instructions for solid dosage forms. If we run out of liquid suspension, we have to go to crushing tablets. That can be difficult for some parents to do.

Next slide, please. Slide 17. The IND written informed consent is going to be difficult with the mass prophylaxis or casualty event. And also following EUA conditions may prove to be difficult to adhere to during a mass prophylaxis or casualty event. There is concern over liability protection that was mentioned earlier. And the communications that are going to have to take place to make sure everybody understands all of these issues is a large challenge as well.

And I'd be happy to take any questions.

CHAIRMAN BOTKIN: Thank you, Dr. Gorman. Questions for Dr. Gorman? Dr. Wilfond?

DR. WILFOND: I have a question and a general comment. I'll do a question first if I can. First of all thank you for your presentation. It was very informative.

Regarding your comment with the challenges for informed consent in these contexts, are there ongoing conversations in other venues to explore other alternatives to address that concern?

DR. GORMAN: I'm sorry, I can't hear anyone in the room.

DR. WILFOND: Oh, can you hear me now? Hello? Maybe she can't -- can you hear us?

CHAIRMAN BOTKIN: Can you hear me, Dr. Gorman? Dr. Gorman? All right. Do we have a phone we can speak directly into?

DR. WILFOND: Jeff, in the meantime, I had a general comment that I could ask to the group while we're waiting for her to come back.

CHAIRMAN BOTKIN: Okay.

DR. WILFOND: One of the things I was struck by in her comments was that I think it actually alludes to one of the points that Dr. Bradley made this morning that his worry about whether we know what the risk of the problem is. And I think

the issue is that I think we need to be clear about the distinction in the risk of the research versus the risk of the event.

What we just heard about was without any knowledge about the likelihood of these activities, the CDC has decided, I think appropriately, to develop a very, very massive huge amount of effort that may never ever be used, which I think is still a good thing. And all I'm trying to point out is this distinction between risk of event, which we only need to have a numerator of one to justify it, versus the risk of research itself, which is a separate question. So I think this could fit under risk of research as we go into our conversation later. That's my point.

CHAIRMAN BOTKIN: Dr. Bradley, you can respond there?

DR. BRADLEY: Just a quick response. Your point's really well taken. And to me, whenever we do research for anything, you need to make sure that there will be a benefit. So the tension I have is what is that benefit? And as you point out it's very difficult to know. But PHEMCE has decided that it's worth spending hundreds and hundreds of millions of dollars because they believe the risk is real.

So I take that cue, and I think these events may occur. Therefore, it's worth taking some risk for the research that's different than the risk that I would take for a vaccine for otitis. So thank you very much.

CHAIRMAN BOTKIN: Dr. Krug and then Dr. Fost.

DR. KRUG: Yeah. Again, nobody understands whether it's ever going to happen, but there have been modeling exercises looking at what might happen if it did happen. The most recent modeling exercise that I'm aware of, and again, I don't have top-secret clearance because then I couldn't tell you anyway, was something referred to as Zephyr, which I believe involved the Bay Area, which killed a lot of Americans for a variety of reasons including the fact that aerosolized anthrax apparently is really bad. It lives in the environment forever, or close to forever. I have no idea of how many people live in San Francisco, but the logistics of getting all the countermeasures out there, even with this incredibly detailed, well-thought-out plan with pre-positioned this and that, it's still enormously difficult to protect the public, which is why the PHEMCE has invested bazillions of dollars. And actually if you look at the Strategic National Stockpile, the component of the stockpile that costs the most are the biologics.

So if someday we could figure out we didn't need the anthrax vaccine anymore because maybe we were all immune, they could spend all that money on something else.

CHAIRMAN BOTKIN: Dr. Fost?

DR. FOST: Norm Fost. I'm confused and I'm missing some very basic point here. The reason we're here, as I

understand it, as Skip and Michelle Roth-Cline outlined, are these complex issues about approving these products in children. But we've heard from Dr. Alexander monoclonal, and we've heard from Dr. Gorman that half a dozen other things have been approved for use in children using other mechanisms.

I'm unclear what the problem is. It sounds like products have been approved. Are we here to make judgments about whether they were approved appropriately or not, whether the process was properly used? It doesn't sound like there's been a big problem in getting products approved for use in children.

CHAIRMAN BOTKIN: Skip, do you want to respond?

DR. NELSON: Norm, the purpose of these three presentations was to give you a feel of the diversity of what's going on, in terms of addressing these problems. But the emphasis on the three questions that we're asking are broader than simply medical countermeasure development. They're still relevant to certain medical countermeasures; anthrax would be one, anthrax vaccine in particular. But they're not relevant to all of them. Sure, there's plenty of medical countermeasures that move forward under our traditional mechanisms. Pralidoxime is a good example that that was approved just using PK data based on industrial accidents related to children being exposed to pesticides.

So, yes, there's a problem in some areas, there's not a problem in others. The questions as you saw them, minimal risk disorder or condition are relevant to this area as well as other areas.

CHAIRMAN BOTKIN: Let me see if Dr. Gorman can hear us.

DR. GORMAN: I can. Thank you.

CHAIRMAN BOTKIN: Great. Sorry about the technical difficulty. We want to go back to a question that Dr. Wilfond had for you.

DR. GORMAN: Okay.

DR. WILFOND: Thank you. Can you hear me now?

DR. GORMAN: Yes.

DR. WILFOND: Oh, good. At the very end of your presentation as you were going through challenges, you were talking about some of the challenges both for the INDs and for the emergency use related to informed consent. And I was just curious whether, other than this meeting, are there places where those issues are being discussed, because I was struck that that seems like a very interesting question of thinking through how to deal with that.

DR. GORMAN: Yes. I think both of those things are discussed on a fairly regular basis in all of our working groups. We're well aware that there are going to be time

limitations and we want to get the medications out to the most people as quickly as possible, so we need to streamline these things as best we can.

So I think these things are considered on a regular basis now in all the public health emergency medical countermeasure enterprise meetings that take place.

CHAIRMAN BOTKIN: All right, Dr. Gorman. Thank you again.

DR. GORMAN: Sure.

CHAIRMAN BOTKIN: All right. We are now scheduled for -- well, we were scheduled for a break back at 10:00. So in deference to our upcoming speakers, I'm going to cut the break down to 15 minutes so folks can return, and we'll restart at 10:45.

[Break]

APPLICATION OF MINIMAL RISK TO PEDIATRIC RESEARCH

CHAIRMAN BOTKIN: Okay. Let's go ahead and get started. And I'm reminded to remind you that given the nature of this meeting, we should not be discussing the substance of the meeting outside the meeting itself. So, there you go.

[laughter]

All right, next speaker is Dr. David Wendler who's going to talk to us about application of minimal risk to pediatric research. David Wendler's head of the Unit of Vulnerable Populations in the Department of Bioethics at the NIH Clinical Center. He's a philosopher trained in the philosophy of science, metaphysics, and epistemology. Dr. Wendler has served as a consultant to numerous organizations including the Council of International Organizations of Medical Sciences, American College of Cardiology, Institute of Medicine, and the World Medical Association. His current work focuses on research in clinical care with individuals who are unable to give informed consent. Dr. Wendler, welcome.

DR. WENDLER: Thanks, Jeff. It's a pleasure to be here.

MALE SPEAKER: Your mic's not on.

DR. WENDLER: Okay. Norm, that's the first time anybody ever said to me that I wasn't talking loudly enough.

[laughter]

Okay. So, what I'm going to try to do is try to provide what I think will be a fairly broad overview of some of the relevant concepts in implementing the minimal risk standard for pediatric research. I think there's some really hard questions here. I'm not going to try to answer those. Hopefully we'll get to those in the discussion in the afternoon. Rather, what I'm going to try to do is try to set up that discussion by trying to provide an overview and hopefully a little bit of clarity on some of the relevant concepts.

So, basically one very simple way to think about pediatric research is to divide all pediatric research, procedures, and studies into two camps: those that are prospect of benefit, basically, and those that are not prospect of benefit. So for some, the procedure of being in this study offers a risk-benefit profile to the child that's at least as good as what they could get otherwise, and I take it, at least with respect to risk and benefits -- we might have other issues about permission and asset -- but with respect to risk and benefits, I take it that these studies are ethically acceptable.

The ethical concern, I take it, what this committee is interested in is what I call net risk research, which is research where there's a prospect of benefit or no prospect of benefit such that the risk-benefit profile to the children who are in the research who undergo the procedures is not, in the

words of some people, favorable. So there's what I call net risk to the subjects who undergo the procedures with the study.

So, I think just a really clear example for us to think about is just imagine you're going to take a couple of children, and you want to do a purely research biopsy. You want to get some tissue. You want to get some blood that you're going to use in the lab for purely basic research. I take it that is what is sometimes called non-beneficial research. All the risks of those procedures are what I call net risks, then, obviously, the ethical question is going to be when are the risks of those procedures sufficiently low that they're ethically acceptable in children.

Just briefly mention for a minute, I think this is, in some ways, a conception more interesting but also problematic category. I think it's also problematic in certain ways for the regulations that we could talk about. I think you could also get a net risk procedure where the procedure offers some prospect of direct benefit, but nonetheless, that procedure can be a net risk research procedure, the way I think about it, if one of two conditions is satisfied. One, if just the potential benefits of the procedure don't outweigh or justify its risks, or even if that condition is satisfied, if the risk-benefit profile of the procedure isn't as favorable as, say, clinically-indicated care, that would still count as a net risk research

procedure, and there'd still be, obviously, ethical concerns: Why are you giving this child something that's less good than they could get in standard clinical care?

So there're two questions that these procedures raise, these net risk procedures. One is just a very simple conceptual question of why is it ethically acceptable in the first place to expose children to net research risks, expose them to risks for the benefit of others. And assuming that we think it is ethically acceptable in at least some cases, then I take it the second question is which risks are acceptable in this context. So, for the most part, I'm going to focus on the second question here, although you'll hear the first one in the background, and I think it's one that we need to spend more time with.

I'll just note that I think some people try to use the minimal risk standard to answer both questions. So what some people will say is a minimal risk procedure is a procedure where the risks are so low and there's absolutely no chance of serious harm that it's acceptable. So, in effect, they're using the minimal risk standard to answer both questions. I think that's a mistake in the end because I think if you understand the minimal risk standard as precluding any chance of serious risk or harm to the child, then you're going to have it so narrow that there's very little research you can approve under the category. We can talk about that.

So, generally, focusing on the second question, most people will say, well, obviously, people probably know a lot of people who don't agree with this. There've been a lot of debates over this over the last 30 years. But there're at least a lot of commentators who will agree that net risk research in children is acceptable as long as two conditions, at least, are satisfied: the research is valuable, it's important, and it's worth exposing children to risks to gain the knowledge that the research is after; and two, that the risks to the children are sufficiently low, and, as everybody knows, in a lot of context, low risks in this regard are termed "minimal risks."

So there's a number of ways you could try to figure out when net risk research satisfies this condition of being sufficiently low risk. One is you could just ask a bunch of people, get a bunch of invested, smart, reasonable people like the people in this room and just present them with a number of research procedures, and ask them, "Is this one okay, is this one okay?" We could just decide whether or not to approve pediatric research in that way.

Although I think that makes sense, I think that there are a number of problems with it. I won't talk about all of them. We could talk about them later if people are interested. But here's at least one that highlights it. We did this survey about 10 years ago when we asked experienced IRB chairs who were

reviewing and approving research with children, and we basically did this: We gave them a list of common research procedures, and we asked them whether they were minimal risk or greater than the minimal risk. What you see here is just this enormous spread. Even in people who had been reviewing, approving pediatric research, there was great disagreement in whether or not these very common procedures were minimal risk or not, and whether or not they were acceptable and approvable. So I think you'd get a lot of disagreement even amongst reasonable and informed people.

So what's going on with the procedural approach? Well, I think there're a couple things. I think there're a couple more. Here are a couple salient ones. One is just that as a matter of human psychology, we're is very bad at evaluating absolute risk. So if somebody says to you, "What do you think about the acceptability of a procedure that poses a 1 in 2,334 risk of moderate harm in children?" If you're anything like me, your initial thought is, "I have absolutely no idea. I have no idea what to think about that. I don't know if that's perfectly okay, if that's terrible; I have no way to really conceptualize the absolute risks of that magnitude." But if we're going to implement this and just do it in a procedural way, that's the kind of question that we're going to need to answer, and I think answering those questions just with our intuitive judgment is really hard.

The second thing is even when we make these judgments, one of the things we do and one of the reasons we're all here is because our ancestors, for evolutionary reasons, got very good at evaluating risks very quickly. And the way we do that is we rely on a number of different heuristics. So one of the very familiar ones is activities, experiences that are familiar, we tend to think that they're not very risky, and things that are new to us, we react to them as though they're very risky. And over the last hundreds of thousands of years, this has been very protective for us and people from whom we evolved. The problem is that this is a particularly problematic heuristic to use in research where a lot of the procedures are new, they are unfamiliar, that's why they're research, but just the mere fact that they're new and unusual doesn't imply that they're necessarily risky. We need to look at the risks, not just the nature of the procedure itself.

So the regulations, I think, did a very clever thing in this regard. They provided a way to try to address these shortcomings with our pure judgment, which is they direct us to make a comparison. Rather than just ask whether a 1 in 2,334 risk of moderate harm is excessive or not, the recommendation is compare that. Take that risk and compare it to some other risks and ask whether or not the research risk is higher or lower than that comparative risk, and as most people here know, the

comparator that the federal regulations direct us to use is the risks of daily life or the risks of routine examinations or tests. So we're supposed to do a comparison between the research risks and those risks.

So the first thing to note here is we now have two definitions of minimal risk, and unfortunately, sometimes these two get conflated. One is the first one I talked about, just whether or not a given amount of risk is acceptable in children, and the second one is now whether or not a particular risk satisfies this regulatory definition. So what I'm going to quickly try to do is clarify what I think this definition intends for us to look at, and then consider very briefly to what extent that clarified definition satisfies the ethical standard for what risks are appropriate and excessive for children.

So a couple ways that I think are mistaken, and I think this is a very common way of trying to implement the minimal risk standard that I think is problematic, which is just to say it's daily life that it directs us to, or routine examinations that it directs to look at. So what does that mean? Well, what it means, then, is whether or not a procedure is minimal risk depends upon whether or not that very procedure is something that children experience ordinarily in daily life. So it's the commonness of the procedure, and I think this is

clearly a mistake, although I think it's unfortunately more common than it should be.

And one example of this, I don't know if people know the procedure Reiki. We had a study about 10 years ago. So basically what Reiki is, you take somebody who's very sick, maybe they're in an ICU bed or maybe they're unconscious. The practitioner puts their hand a couple of inches from the skin of the patient, and the goal of Reiki is for the practitioner to draw out the negative energy from the patient that's making the patient sick and infuse positive energy into the patient to help cure the patient. That's, as far as I understand it, the way Reiki works.

Well, now, clearly Reiki is not something, at least in D.C., that we ordinarily experience, that children ordinarily experience, but that doesn't make Reiki more than minimal risk, right? It's not the fact that children don't ordinarily undergo it; it's something about the risk level. If anything is minimal risk, a study of Reiki is minimal risk. So the procedural standard isn't the right way to go.

A second one that's closely related to it is what I call the type of risk standard, which is to think whether or not a risk of harm is minimal risk or greater than minimal risk depends upon whether or not children ordinarily face that type of risk in daily life. So, bruises. Children are always facing

bruises, falling off their bikes, playing sports, fighting with their siblings. So on this view, a bruise would be minimal risk because it's ordinary type of risk because it's ordinary type of risk, and a type of risk that children don't ordinarily face would be more than minimal risk. And I think the Reiki example here is a nice way to show that that can't be right either. The risk of Reiki is to have the energy flow go in the wrong way. That's the risk of Reiki.

Now, whether or not that's minimal risk or not, I don't know. But it's not just the fact that children don't normally experience that kind of risk. That doesn't make it more than minimal risk. We have to look at what the chances are that's going to happen and how bad it would be if it happened.

So what's going on here? Well, the point is what that we're trying to do, I think, is we're trying to avoid exposing children to excessive levels of risk in the process of collecting data that we think is valuable. So that suggests to me it's the level of risk that we care about. We want to make sure that the level of risk that the children face isn't excessive.

So the way that suggests to me is what we do is we want to look at the level of risk from the research procedural study, compare it to the level of risk children face in daily life, and see how those two compare. People know a lot about

this. Loretta's here, who's done a little work on this. That what the minimal risk standard doesn't tell you is the risk of which children. And I think, by now, there's fairly broad agreement that what we should be looking at is something like the risks that average, ordinary children face in daily life. So that's what you might call the objective interpretation. So what we're supposed to be doing here is looking at the level of risk that average, ordinary children face in daily life, and see how the risks of the research procedure in question, say the biopsy I mentioned a minute ago, how those levels of risk compare.

And so then this next question. So that's basically what I think to be the right way to think about the minimal risk standard. The second question: is that going to get us risks that are ethically acceptable? That's how you satisfy the regulatory definition. Is that definition clarified, as we just said, going to capture what's ethically acceptable and what's not ethically acceptable. And I think there are at least two worries or reasons to think it might not until we limit it even further.

The first one is all it talks about is the risks of the activities of daily life. But notice that a lot of the activities of daily life that we think are appropriate for children, we think are appropriate not because the absolute risk

level's acceptable, but because the activity offers potential benefit that we think justifies the level of risks of the activity. So my neighbor kids, they go mountain biking on the weekends, and they go skateboarding during the week on the sidewalk. Their parents, I think, are very reasonable, caring parents, and it's not that the parents think just the risks of mountain biking are okay; they think, no, mountain biking is kind of risky, but this is a really valuable activity for my children.

So there, why the risks are acceptable is because the activity itself offers potential benefit. So I take it that that same level of risk isn't going to be an appropriate standard for evaluating acceptability of research that doesn't offer the children potential for benefit. So we don't want the risk of activities where we think they're acceptable in daily life because of benefits to the children. So that's the first caveat.

The second one is just the simple fact that the risks of daily life sometime pose risks that are, we think, unacceptable to children. There's a very famous paper on the literature by a Canadian group that talks about the minimal risk standard, and they say the risks that children face in daily life are normatively acceptable, and I always think of that as the Canadian view of the world. That might be true in Canada,

all right. If a risk exists in a lot of the children in Canada, it's probably acceptable. Unfortunately, we haven't gotten to that point yet in the U.S.

[laughter]

We're trying to catch up to Canada here. So there're some risks that we just don't think are appropriate, so we shouldn't be using those to judge the ethical acceptability of pediatric research.

So here's the way I think about this, is, basically, the caveat suggests that what we need to think about is not all the risks of the activities of daily life but we need to limit it in two ways. First, we need to think about just activities that we think are appropriate or acceptable in daily life, and secondly, we need to limit it to activities that we think are appropriate and acceptable for children in the context of activities that are designed to benefit others. That's the relevant comparator. That's what we are worried about with research. So we don't want mountain biking if we think the risks of mountain biking are justified by potential benefits to the children. We want activities where we think the risks are acceptable even though the benefits are going to others. That's roughly what the non-beneficial research example is.

So there're lots of examples in this where we think it's reasonable to allow children to face risks for the benefit

of others. Charity car washes, putting your kid in the car to help the neighbors, selling cookies for Oxfam, telling your 13-year-old to go shovel the neighbor's sidewalk, are all cases where you're having your child, I think, reasonably face some risks that benefit others. So I think those are the activities, the kinds of activities that we should focus on.

This is just quickly some data from two studies that we've collected recently, I think, that shows that if you talk to parents and children, they actually regard this as a reasonable way to think about minimal risk. They actually think in terms of comparing charitable activities to research, and in a lot of these cases, the parents and children we talked to were at least as willing, and, in a number of cases, more willing to participate in research to help others than they were to participate in charitable activities. And here, we talked to some adolescents about what they thought about facing risks to help others, and a lot of them, they thought was a very important thing to do. They were very proud of being in this situation, being able to help others. So I think there's this way in which children actually can recognize that they're -- can make that valuable contribution by being in this kind of research.

So how do we implement this? So one way might do this is we have the risks of daily life. We're supposed to compare

them to the risks of research. We might just compare them, just ask reasonable people, again, reconvene our reasonable person group and just ask that we compare them. Here's a research, lumbar puncture risk here, less risky than having a child shovel their neighbor's sidewalk. A bit of way to go but, again, I have no idea how to answer that question, and the other worry I have is that the heuristics that I talked about are going to kick in. Well, I'm used to my kids shoveling sidewalk. We're used to that, so I don't think it's risky, even though I have no idea, I've never seen data on the risks of a 14-year-old shoveling the sidewalk. Lumbar puncture, that's unusual, so I'm going to put this fairly risky, even though, again, I've never seen any data on 14-year-olds undergoing a lumbar puncture.

So I don't think that's going to get us very far in terms of addressing the concerns that I mentioned before. So our approach and what we've been thinking about is trying to figure out more systematic ways to guide our judgments on what risks are acceptable or not in pediatric research. And then the idea would be we have a method, see what the method tells us, and then make our judgments based on the results of that method rather than just bear the intuitive judgments.

So, I'll just go through a simple part of this very quickly. There's a lot more to it, unfortunately. So part of it is just if we're going to implement this in a systematic way,

the risks of daily life standard, remember, it's comparing the risks of daily life to the level of risks of the research procedures. You need at least three things to do that. You need to know the data on the risks of daily life, you need data on the risks of the procedures, and you need a way to compare the two.

I give talks on minimal risks to investigators a lot who complain about IRBs, and how IRBs are so cautious, and they think that all the procedures are more than minimal risk. And then I ask the investigator, "So, what data did you present to the IRB to try to convince them that your IV glucose tolerance test is minimal risk?" And they said "Data? We didn't do that. We just told them we think it's minimal risk." Well, why would you think that's going to be convincing? This is supposed to be an empirical standard. We need the data. So I think we need to do a much better job at collecting data, both on the risks of research procedures and the risks of daily life, and then we need a way to compare them.

So the first two, we just need to collect the data. It's hard, but I think it's an important job to do. I won't talk about that today. I'll just talk very briefly about a way we've been thinking about to try to compare them once you have the data. So this is what we call the systematic evaluation of research risks.

So the general idea is that risks are a function of roughly two things: the magnitude of the harm if it occurs, and the likelihood that that harm is going to occur as a result of a research procedure. So if you take LP, imagine that the risk is a post-LP headache, and then that'd be the magnitude, how bad the post-LP headache is, and then there's some probability that you're going to get a post-LP headache if you have a lumbar puncture, and we just have to collect a lot of series of data to find out what that likelihood is.

So you got two different things. You've got the magnitude and likelihood on both sides, and so the idea is if you want to compare them, I think for the most part, we can talk about if there's some caveats, but for the most part you compare the likelihoods to likelihoods and magnitudes to magnitudes. So, for the most part, comparing likelihoods to likelihoods is relatively straightforward. It gets complicated when you have likelihoods that are relatively similar, so in this example, is a risk of an LP headache of 1 in 3,000, is that the same as a risk in 1 in 3,200? I mean, they're not exactly the same, but normatively about the same, and when do you have a sufficient numerical difference to make a normative difference.

Comparing magnitudes is harder than that. So, to take an example, is experiencing an LP headache worse than an ankle sprain? It's hard to know how to answer that question. So what

we've been trying to focus on is that second question, and providing some methodology for doing that. Basically, harm is coming off spectrum from very, very small to death and permanent disability, and there's a lot of data in psychology that we're pretty good at manipulating between four to about eight categories, and once you give human beings more than about eight categories, we start getting really confused.

So we wanted to try to split up the spectrum of harms within that number, so we did a lot of focus groups, and what we came up with is these seven levels of harm. So you don't have to memorize these. Basically, these are just the levels going to the top, negligible, to the bottom, catastrophic. There're are examples of each, and then from the data that we've collected thus far, we have some data from some of the activities of daily life what the likelihood of experiencing of harm of that magnitude is from the activities of daily life.

And so I think for the purpose of right now, you don't need to think about this too much, but basically, this is just the way that you would make the assessment according to the systematic evaluation of research risk. You try to categorize the magnitude of the harm of, say, the post-LP headache, or, in this case, an infection from the biopsy, you categorize that, and then you find out from your data what the chances are of that occurring as a result of, say, the biopsy or the LP, and

then you compare the likelihood of experiencing harm of that magnitude to the likelihood from the table I showed you just previously of experiencing a harm of the same magnitude from one of the activities of daily life. So that's roughly the general idea for how it works, although I realize that was too fast. We can talk about it if people are interested.

So just a couple of comments on that. One is that this process is complicated to a large extent, so I don't think it's something that IRBs are just going to be able to do at convened meetings. I think if we're going to implement something systematically like this, I think what we need is we need committees like this one that are going to put together analyses of common research procedures, and then IRBs can then take those as judgments for the risk of those procedures.

As I mentioned before, we need data. We need a lot more data than the data we've got. Also important to realize that there're a number of places in which this process still requires normative judgment. I mentioned before you need normative judgment of whether two likelihoods that are close but not identical are normatively equivalent. You need judgment to figure out how bad is an ankle sprain. Where do you put that? Is that a negligible or is that a moderate harm? We need judgment there.

So there's a couple places where you still need to make judgment. I think that those are probably ineliminable. I think it may be a good thing that they are. And then we just need more work. We can talk about this, but we need more work on actually how to implement this method within more complicated cases.

So one last point I want to just make is that I don't know people think, this one always seems controversial when I talk to people about this, but it seems to me this is one that others think seems controversial, and I understand. This just seems to me like it's got to be right but people think it's controversial, so I'd be interested in people's thoughts, which is if you look for the most of the literature of minimal risk, it seems that there's implicit assumption that the level of harm that we use for evaluating minimal risk is constant for all children. Whether the children are 6 months old or 17 years old, we're going to use the same threshold or the same limit for the risks to which we can expose them.

And if you think about the comparator to daily life, that seems really puzzling, right? I don't think any reasonable parent says that the risks I can expose my 17-year-old to are the same risks I can expose my 6-month-old to. They're just completely different, a 6-month-old and a 17-year-old. Why are they completely different? Well, one, they're more mature, but

in this context what I think is really important is that 17-year-olds can understand a lot that 6-month-olds can't understand. And in particular, they're good data that your average 17-year-old probably understands about as well as an average adult does. You can decide whether you think that's a good thing or a bad thing, but I think those are what the data are, and so I think that the ethical worry about exposing a 17-year-old to risks for the benefit of others is significantly different than the ethical concern of exposing a 6-month-old to that same level.

So here's what you'd do. If you did it just with one risk level, you'd have to pick some risk. So maybe what you'd do is you pick 10-year-olds, and you say, okay, 10-year-olds are going to be our level for the minimal risk standard, whatever risks 10-year olds face in daily life. Well, the problem is I think that might be under-protective and overprotective. When you come to 6-month-olds, the risks you'd be willing to expose 10-year olds to might be too high for a 6-month-old. On the other hand, as I mentioned, teenagers can understand, typically, the research you're proposing to them, so the limits that we put on 10-year-olds might be overly restrictive when it comes to a 17-year-olds.

So what should we do about that? One thing we could do is you could just have a sliding scale, each year that the

children gets older, you can expose them to greater risks. I think, theoretically, that makes sense. I think in practice, it would probably be a disaster. One is it's really complicated. Two is, as this meeting attests, we're having enough trouble figuring how to implement one minimal risk standard; having 17, 18 of them probably would be terrible. And secondly, I think it misses the point that it's not just slight increases in maturity that make a difference, it's certain thresholds, and I think the most important threshold is whether or not the child can understand the research to the extent we think they need to understand to a degree to undergo it.

And the data that we have suggests that probably happens sometime between 12 and about 15. And so I think there are two ways to do this. One is we could just pick a date like we do for a lot of other things: when you can vote, when you can drive. We know they're arbitrary to a certain extent. But we could pick an age, 13 or 14. Another thing I've suggested in some of the NIH studies is what you do is if it's slightly riskier than you think is acceptable for an 8-year-old, what you do is you have an independent person assess each individual child, and if they can understand the study and they agree to be in it, then you're going to allow slightly greater risks for those children. So, in some cases, you might have an approach where you just evaluate specific children.

So, just to summarize very briefly, a couple of things I wanted to highlight. One is, I think the important thing is when we're trying to evaluate minimal risk in children, we're trying to evaluate the acceptability of biopsy, or an LP, or medical countermeasures in children, doing research on those things on possible vaccines, it's the net risks; it's the risks that research adds to the children's lives that's not compensated by a potential benefit for the children. Those are the risks that we should be focusing on. And it's the level of those risks. It's not the type of those risks. It's how that level of added risk compares to the added level the children typically face. I think, as I've just argued, that I think we should be willing to allow greater net risks in, say, 14, 15, to 18-year-olds and probably less in children under about 2 or 3. And then finally, I think there's a lot of work that still needs to be done if we want to really implement this standard systematically.

CHAIRMAN BOTKIN: Thank you very much. This, of course, is getting into the meat of the issues that we're going to be discussing, and so I want to restrict the conversation at this point for questions for Dr. Wendler. So, Dr. Wilfond?

DR. WILFOND: David, first, I apologize for having my back to you right now.

[laughter]

But I can't talk in the microphone without doing it easily. You know, David, first of all thank you for that presentation and for all the papers you've written on these variety of topics. It was fun looking at the exchange between your paper that was a semantic valuation, and then Skip and John's reply to that regarding the normative issue. And what I was struck by your presentation today regarding the issue of the different age standards for minimum risk is that that was essentially a normative claim. And it occurred to me that I wanted to see whether you thought that your attempt at talking about the age distinction really does illustrate the normative dimension of risk, and whether or not you actually think that a systematic evaluation approach, and how would that apply to this issue of age relationships? Or is it just an example of the normative aspect of it?

DR. WENDLER: So just to emphasize what you said, I think, absolutely. The claim I made that I'm proposing is that we should have, in a sense, different risk standard for very young children and very old children. That's not an empirical claim at all. I take it that's completely a normative ethical claim based on what I think makes ethical or normative sense, and so that's not a claim that you can, as far as I can tell, maybe I'm not imaginative enough, but that's not a claim I could

see any way that you could use something like the SERR method to test.

Rather, if you agreed with that, you'd have to have a normative, ethical, philosophical discussion about whether or not that approach makes sense, and then if you agreed that it did, then you could use SERR to implement the two different standards, and you just plug in different numbers for what level risk acceptable, when you're evaluating a study for, say, 15-year-olds, and you'd plug in much lower risks when you're evaluating whether a study of, say, 2-year-olds is a medical risk.

CHAIRMAN BOTKIN: Dr. Kopelman.

DR. KOPELMAN: Thank you for your presentation.

MALE SPEAKER: Microphone.

DR. KOPELMAN: Oh, thank you. Loretta Kopelman. Thank you for your presentation. As you know there are two standards. One is the everyday risk standard, and the other is the routine examination standard, which you entirely left out of this presentation. I believe the everyday risk, the risks encountered in everyday life, is a very ambiguous standard. It can mean all the risks some of us encounter, which would include firefighters, and jet pilots, and soldiers in Afghanistan, and I'd say that's an extremely high risk for a so-called minimal risk.

Another way to understand it is all the risks all of us encounter. It's not keyed to children in the definition. And that is, in a way your presentation shows, very, very difficult to determine what all the risks all of us encounter in daily life. I think it makes it almost hopeless. But the third interpretation is all the minimal risks of daily life, which, unfortunately, makes it circular. And I wonder if when you say what we should focus on are the acceptable low risks for average kids, you really aren't very dangerously close to that circular definition of the minimal risks of daily life, but we're out to define and find a standard for minimal risks, to say the acceptable low risks define minimum risks is a tautology and not really a standard. I also think thinking of charity is a wonderful metaphor, but I'm not sure it's an analysis. It's neither necessary nor sufficient for children to feel good about making a charitable contribution, so I think it's a good metaphor, but I don't think it's analysis.

And finally, with to respect to your SERR, I just know that I agree with Skip on this is a moral judgment, and that there are a lot of normative judgments being involved, including the grouping of the harms, so I don't know if you have anything you want to reply, but I suspect you do.

DR. WENDLER: I think I definitely agree with you on the last thing. I thought I was trying to highlight places

where there were normative judgments made. I'm not sure what you mean when you say "low risks." I don't remember saying that. When you said I might be circular because I'm talking about the low risks --

DR. KOPELMAN: You said "acceptably low risks." You say, in your slide, "acceptably low risks," that that's what we should aim for.

DR. WENDLER: Yeah, I think that's that just the intuition that people have. If you talk to people at a cocktail party, "When is this kind of research okay?" they'll say, "when the research" -- at least the people I talk to. Maybe it's the parties I go to.

[laughter]

"When the research is valuable and the risks are acceptably low." And so then the challenge is, how do you determine when the risks are acceptably low? And when I went through that, I don't think I used circular terms like minimum or low. It's the risks of acceptable charitable activities for children roughly that age.

DR. KOPELMAN: But the word "acceptable" is a heavily normative term.

DR. WENDLER: Absolutely. Absolutely. I completely agree.

CHAIRMAN BOTKIN: All right, I have Dr. Fost, Dr. Krug, and Dr. Grabenstein, and then I'm going to cut it off at that point, so, Dr. Fost.

DR. FOST: David, thanks. It's a terrific summary of a lot of complicated stuff that you've helped us a lot over the years in explicating. Let's stipulate that the comparison with charitable activities is a good one, and I think it is, and I think it's about the only rationale for exposing children to things that have no direct benefit to them. And let's also stipulate, and I agree with you, I'm not for sure about this, that the risk should be assessed for that individual child, not for children as a whole, not even 10-year-old children, but that specific child, because there's 10-year-olds for whom a certain activity would be profoundly upsetting and distressing, and others for whom it would be really cool and fun.

And our IRB has always required our investigators to do that, not to say you can do these procedures on the next hundred 10-year-olds that you can find, you have to assess each one, like the CAT scan. You have to do a pretest of the kid in the CAT scanner, to see if he or she really is okay. Let's just stipulate, because I agree with you about all that, that that would seem to exclude any non-beneficial research on infants. The charitable stuff doesn't apply.

That is, a 6-month-old doesn't learn anything from having himself stuck, unless you're going to, 10 years later, say, "You know, when you were an infant we stuck you full of needles." That's number one. And number two, the anxiety level that a 6-month-old or the 18-month-old experiences from having a needle stick is off the charts. That is, they scream and they yell, and you have to hold them down, and we would never allow a parent to expose their child to a charitable activity that was met that screaming and yelling and "Let me out of here," that is, protesting in every way imaginable.

So my question is whether your analysis really precludes any kind of non-therapeutic research, let's just say needle sticks for pre-cognitive children.

DR. WENDLER: Great questions, Norm. I want just say two things quickly. One is, I don't think this approach precludes non-beneficial research on 6-month-olds. I think what I didn't do, and what you would need to do to answer that question is you have to ask the question: Why do we think it is acceptable to expose children to risks, say in charitable activities? I think one answer people give is because they've learned things as a result. I think to the extent that that's right, it's great, but I don't think that we require that. I don't even think we think that's a necessary condition. Imagine that your infirm neighbor really needs help, but you think, in

this case, your child's not going to learn anything from it. I think you still might say, "Look, they need the help. The risks to you are really low; you're going to do it. And you're going to do it even you're going to scream and kick a little bit while you're shoveling their snow." I think it's still something that we do. Again, we can talk about why, I think there is a justification, but I think, in a sense, it's deeper than just "They'll learn from it." I think basically what it is, is that there's a value in that contributing to valuable activities whether, in some cases, they embrace them or not.

And then in terms of the screaming part, I think what we're assuming is, that screaming is very acute, short-term, and not a long-lasting harm. And if that's right, I mean, they're going to scream, and they're really upset for the next five seconds, I think that turns out actually to be a very low harm. But if that's going to traumatize them, like putting some kids into an MRI and it precipitates panic attacks, then that's really bad and we shouldn't do that.

CHAIRMAN BOTKIN: Dr. Krug.

DR. KRUG: Steve Krug. That was a magnificent presentation. I wanted to comment briefly on the concept of allowing greater net risks in older kids and adolescents. I mean, that reflects our practices today in the average clinical setting. So older children who have diseases, we get their

assent during the process. We just don't do it to them, even if their parents say it's okay to do it to them. Where I work we actually allow, and part of this is because there's a greater risk of disease and because there are concerns regarding access to care, we allow teenagers to present to the emergency department, and we do not need their parents' assent. We are actually not required to let their parents know that they are there because that's actually what the law says. And it's, in part, because the risk is greater for things like sexually-transmitted disease and pregnancy and whatnot, but also because these are older children, young adults, who actually understand and are capable of doing that.

So I think, just as an example, the same concept could be used, and is being used, in terms of engaging teenagers in various things, including research, that requires their ability to understand. Are all teenagers the same? Absolutely not. There are 17-year-olds who kick and scream when we draw their blood, but you make a general assumption that most of them do understand.

CHAIRMAN BOTKIN: Dr. Grabenstein.

DR. GRABENSTEIN: David, thank you for the presentation. You spent most of your time talking about age as a gradation, 1-year-olds to 17-year-olds with some stops in the middle. What about geography? You know, in the medical

countermeasure realm it presupposes attacks. We've seen it in Washington, New York with biological weapons, explosives in London and Madrid, and now Austin, children among the casualties of each case. Is there a dichotomy to be made between metropolitan area kids and rural small-town kids, and does that apply here? How would you see that apply to this model?

DR. WENDLER: In terms of implementing minimal risk standard, to me, whether or not that be relevant, it's asking the normative question of do you think that that difference, the geographic difference, makes an ethical difference in the extent to which you think it's acceptable to expose those children to risks for the benefit of others? And as Loretta said, I think the reason why I focus on the charitable participation center is just to keep in our heads that what's being done here is risks to them for the benefit of others. I think that's the crucial concept.

And I take it, just having not thought about it, though, off the top of my head I would say that wouldn't make a difference for me. It wouldn't be clear why the fact that they live in the country would be a reason why it would be acceptable to expose them to a greater, or, say, lesser risks, for the benefit of others. Now the risks that they might face might be different; it might be because they're more dispersed the chances that any particular kid's going to get infected are

lower than if they're living in Manhattan or something like that. So maybe the risks of the actual event would be different, but I don't think that the risks that you could acceptably expose them to in the context of doing research would be different.

CHAIRMAN BOTKIN: Dr. Glantz, something quick here.

DR. GLANTZ: Yes. One of the factual statements that children doesn't mean under 18, for regulatory purposes, it means children who can understand the risks and benefits, and who can otherwise consent to the procedure is not a child for purposes of the research under the regs.

The question I wanted to ask you, though, is actually quite brief. Your answer might not be so brief. Which is, you said at the end that the older kids understand more, and therefore it might be okay to use older kids, but what does that have to do with the risks? I understand the understanding part, but it seems to me the risks don't change because somebody understands something.

DR. WENDLER: Right. Well, my initial thought is that I don't think this is the entire ethical issue. I think even research, non-beneficial research with competent adults, raises important ethical issues, even when they consent. But I think that, in effect, the special ethical concern or the added ethical concern that pediatric research raises is the fact that

we’re often exposing individuals to risks for the benefit of others when the individuals who are being exposed to the risks don’t understand it and can’t meaningfully agree, “I’m willing to face these risks for the benefit of others.” I think that’s what raises really serious ethical concerns in pediatric research. And so the idea is that if the child can really fully understand the proposal, and says, “Yes, I’m willing on take on these risks for the benefit of others,” then even if the risks haven’t changed, the ethical concern is dramatically lower. It’s not zero, but it’s dramatically lower than if you’re doing it in a child who just can’t understand, or even an adult who couldn’t understand.

RETHINKING RISK EVALUATION IN PEDIATRIC RESEARCH

CHAIRMAN BOTKIN: I want to thank you so much. Our next speaker is John Rossi, who's going to be talking to us about rethinking risk evaluation in pediatric research. John Rossi is an Assistant Professor at Drexel University's School of Public Health and Associate Director of the Program for Public Health, Ethics, and History. Formally trained in veterinary medicine and bioethics, and has completed postdoctoral fellowships in ethics and public health at Drexel and the U.S. Food and Drug Administration. John's scholarly interests include research ethics, philosophical issues in risk assessment and communication, animal ethics, and ethical theory. Dr. Rossi, welcome.

DR. ROSSI: Thank you. Can everyone hear me okay? All right. I'd like to thank FDA and Skip for inviting me here today. I'm very pleased and honored to be here, and to the Committee, I appreciate your time and attention, as well the audience. I was tasked with delivering a lecture on the interpretation of the risk categories in federal regulation with specific emphasis on minimal risk, so I'm going to try to stick to that. I'm not going to talk about the general normative ethical justification of non-beneficial pediatric research whether and when it's justified. I'm also not going to talk about the other risk categories: greater than minimal risk,

minor increase over minimal risk, or greater than a minor increase over minimal risk, though I suspect that the arguments that I present here today will apply to those categories as well.

And we've had 30-plus years of discussion about this, so one might reasonably ask what more can or needs to be said, and multiple people have asked that. I do think that more can be said, and, in particular, I think most, perhaps all even, of the existing interpretations of minimal risk on offer, perhaps with the exception of the scrupulous parent standard, suffer from a common conceptual underpinning and a common conceptual flaw. I call them the finest approaches, and I'll talk more about that in a few minutes. I'm going to spend most of my time making that critique, and finishing up, I'm going to sort of suggest or look towards what I think might be an alternative way to conceptualize risk evaluation, which is what I call a dispositional, deliberative approach.

So two pragmatic points. I'm going to assume audience familiarity with the regulations as well as a lot of the proceeding bioethical debate, and, unfortunately, I just don't have time to get into that. And a quick point on pragmatics. So I do think that pragmatics are very important, and when I say pragmatics, I mean such things as how long is it taking IRBs to get through deliberations; they're obviously pressed for time.

If we interpret the risk categories as one way versus another way, is it going to affect how long it takes? Is a particular interpretation compatible with expedited review? What about inconsistency between IRBs? How do we handle that issue and so forth? I do think those are important. I don't, unfortunately, have time to get into them.

And admittedly, I'm feeling a little insecure because Dr. Wendler pointed out some criticisms of intuitionist approaches in his lecture at the beginning, and the approach that I'm going to recommend is, in a way, intuitionist. Now, an important point of distinction is that it's not bare or naked intuition I'm suggesting we rely upon. It's a little bit more complicated than that. It involves making evaluations under appropriate conditions, perhaps including probabilistic information, or definitely including probabilistic information. My suspicion, though I don't have time to get into those pragmatic issues, is that most of what's likely to be raised as an objection to the approach I'm recommending could probably be handled. I don't expect everyone to take my word on that, but I encourage you to ask questions or seek me out for discussion, and I'll try to met any objections you may have.

Now a second more general point I want to make about pragmatics. My impression, being fairly familiar with the pediatric bioethics literature, is that discussions are

oftentimes very pragmatic and very on-the-ground, and there certainly are reasons for that, but at times, I think it's important for us to step back and ask some more conceptual questions because, at times, I think we put the cart before the ox. And specifically, for me, the best procedural way, the best order of operations, is to start by asking, "What do want these risk categories to do, and what's conceptually the most defensible way to think about making these kinds of judgments?" And only after we've done that, or only after we've made sufficient progress on that front, do we turn to the issue of pragmatics.

One might say that an approach that's concrete or easily implemented isn't really worth much if it's based on an unsound conceptual underpinning, if it either was too conservative, or if it would allow for risks that were excessive. And that's a pretty strong claim, but might be true. A slightly weaker claim would be something to the effect of "Maybe there's a balancing act that goes, that we have to get into." Is it better to have a conceptually sound interpretation of minimal risk that may lead to some inconsistency in application, or is better to have an interpretation that may lend itself to a lot of consistency and ease of use but suffers from some conceptual problems? I won't presume the outcome of

that discussion, but that question needs to be asked, and I don't think it's asked enough.

So let's start here. What is the concept of minimal risk and its derivatives such as a minor increase over minimal risk supposed to represent? I see two options. One is the judgment of risk magnitude, and the second is a normative justification or normative judgment about the ethical permissibility of non-beneficial pediatric research. And on either of these conceptual readings I would suggest that we need a different approach to risk evaluation as compared to predominant approaches, and under predominant approaches the include the daily life and routine examination interpretations of minimal risk, but also the more recently proposed charitable participation standard.

So let's look at the risk categories as judgments of risk magnitude. To me, this is the most intuitively plausible way to understand such terms as minimal, or greater than minimum, or, for that matter, moderate, severe, high/low, etc. This is how we use these kinds of words in ordinary language; they denote magnitude, whether we're talking about harm, or risk, or something else. I would also suggest that this is consistent with how the National Commission used these kinds of terms in their report "Research Involving Children." If you go back to that report, if you look at Chapter 8 where they located

most of their philosophical discussion, they, after a lengthy discussion, arrived at a considered judgment, that non-beneficial pediatric research can be ethically acceptable when the risks are low. They explicitly considered and rejected the possibility or the position that non-beneficial pediatric research is never justified. And the regulatory definition of minimal risk that we have, in my view, is best looked at as a specification of this general idea of low risk, so it denotes risk magnitude.

We can then take another step and note that almost all proposed interpretations of the risk categories that we have are definitional. So if they define minimal risk and the way that they define it is in terms of a set of risks: daily life risks, however understood; the risks of routine examination; or the risks of charitable activities.

And there’s two main philosophical problems with this approach, and they're related. The first is what we could call the Goldilocks problem. So there’s no definition that’s been proposed that seems to get it exactly right in terms of picking out just that set of risks that conforms with our intuitive judgments of what’s minimal. So let’s just put a couple of examples here. The most famous would be the relative interpretation of daily life. This says that minimal risk is that the individual child being enrolled in research faces in

their daily life. And the subject of two very well-known philosophical criticisms: the first is a criticism from a principle of formal justice which says if you're going to treat like cases similarly, and if we're going to treat cases differently, there has to be a morally relative difference.

Well, this interpretation would allow different groups of children to be exposed to different risks, right? Healthy children versus ill children, children living in safe environments versus children living in unsafe environments. And many people seem to think that there's no morally relevant difference that would justify differential treatment; although I will note that, as an aside, that there's been some recent qualifying defenses of the relative interpretation that I think deserve our attention.

The second objection to relative daily life, which, to me, is more immediate and ultimately gets at the heart of the issue, is that if daily life risk just means the risk the individual child is facing, then for some children, they're going to face really high risks in their daily life. Think of someone who lives in an unsafe neighborhood, a child who is exposed to a high risk of violence, for example, got very bad outcome, right, death or physical injury at potentially a high probability, so that gets us very far away from what the

original intention of what this minimal risk concept is supposed to represent. It's supposed to represent low risk.

Now, in order to solve this problem, we could go to a routine examination standard, but that's been criticized for going too far in the opposite direction, that it would be too conservative, and the way to frame this in terms of risk magnitude would be to say that there are risks that are greater than the level of risk faced in routine examinations, that nonetheless, we may be disposed to evaluate as minimal. Even the absolute daily life interpretation has been criticized because some risks that even average, healthy, normal children face in their daily lives may be too high. And while I haven't seen the argument made in the literature, there's no conceptual or logical barrier to someone who says, "Well, I recognize that most of these daily life risks are minimal, but I also think that this risk is greater than most of these daily life risks." I also think that happens to be minimal, too.

So most recently, we've had a charitable participation standard proposed, which is a definite improvement because it offers greater normative parity to non-beneficial research than either daily life nor routine examination risk because, in charitable activities, there's no direct benefit, other than, perhaps, moral development, and the risks are avoidable, whereas in daily life risks, for example, there is compensating benefit,

or they can't be avoided, or it's very difficult to avoid them. But, we may still look at the set of risks a child encounters in a charitable activity, or a set of children encounter in charitable activities, and look at that set of risks and say, "Well, I think some of those are minimal, and I think some aren't." So we've got a problem of fit, and what do we do with this?

One potential response is to say that if you favor one of these definitions, that if somebody's intuitive judgment differs from that, they're wrong. The definition is correct; your intuitive judgment is wrong. But that merely raises the questions of why we should privilege the stipulative definition over our intuition; what are the reasons for that? And so here we can make use of something called the open question test or open question argument, which is a very famous argument in moral philosophy. It was first proposed by a British philosopher named G.E. Moore about a century ago, and there's various ways to understand what this argument is supposed to be getting at. For me, I think the best way to look at it is it helps us assess whether two terms have the same meaning. It also helps us to assess whether a particular ethical term is compatible with a sort of a reflective judgment on our use of autonomous evaluation and endorsement of things, which a lot of people

would take to be a requirement of any sound ethical theory or ethical term.

Now, Moore was particularly concerned with what are called naturalistic theories of ethics, so theories that would say such and such was right because it’s natural, you know, I don't know, eating meat is right because it's natural or something like that. But also with theories that would define the term “goodness” in naturalistic terms, and there were a lot of utilitarians around this time and beforehand who would say things like “Well, goodness is just happiness,” or “Goodness is just pleasure.” And Moore thought this was a mistake, so he came up with a kind of clever little linguistic argument. He said, "Look, if these two terms mean the same thing, if goodness and pleasure, for example, mean the same thing, we should be able to use them interchangeably in a sentence with no loss of meaning.”

Well, you can run that argument on any evaluative term that you like, including minimal risk. So if we have two sentences here: “I know Risk X is encountered in daily life, but is minimal,” and then, “I know Risk X is encountered in daily life, but is it encountered in daily life?” These two sentences don’t seem to mean the same thing, and the second sentence is closed in the sense that if we encounter a risk in daily life, then we know that we encounter a risk in daily life. That’s not

an open question, whereas the first question is both intelligible and open to doubt. Okay, I know this risk is encountered in daily life. Is it minimal? I'm not sure. I need to think about it, or I need some other argument that's going to tell me that.

So at first glance, at least, minimal risk doesn't appear to be definable in terms of a set of risks. Now there's an important caveat to this. We've had 100-plus years of discussion of this argument, a fair bit of it critical, and subsequent philosophers have pointed out that, at times, two terms can be identical even though in ordinary language use they don't seem to mean the same thing. And the most famous example here is water and H2O. We happen to know that H2O and water are, in fact, the same. H2O is just the chemical formula of water. But some philosophers, nonetheless, seem to think here they feel that in ordinary language water and H2O don't mean the same thing. Now I'm not sure if they're right about that, but let's assume that they are. In the case of water and H2O, we actually have good arguments that tell us they're same thing, namely arguments from the natural sciences, from chemistry, right? That's how we know water is H2O.

We have no such arguments in the case of minimal risk. There's no argument from the natural sciences; there's no argument from moral semantics or anything of the sort that's

going to say “Oh, minimal risk is, in fact, identical to daily life risk, routine examination risk, charitable activity risk, what have you, even though they don’t seem to be the same in ordinary language.” We have no such arguments.

So this Goldilocks problem, coupled with this open question failure, indicates two things to me. The first is that it’s not philosophically plausible defining minimal risk as a set of risks. We can do it. Maybe there’s some other argument, some pragmatic argument that says we should do it anyway, but if we’re looking at just what’s conceptually plausible, we can't do it. Now, we still may use charitable activity risk, daily life risk, or routine examination risk as examples of minimal risk. I don’t deny that many of those risks would be examples of minimal risk. But if we’re looking for a conceptual definition, those terms aren’t going to stand in for it. And once we recognize this, we may then ask, "Well, is there any other kind of determinant or definite definition that we can come up with that’s going to tell us what minimal risk is?" And I doubt it, at least not if as we understand it as a judgment of risk magnitude.

And I say that for two reasons. Judgments about risk belong to the study of prudential value, that is, what affects our welfare, what's conducive to our well-being. And in this category, we also have judgments about benefit and harm. And

prudential value judgments, I would say especially about the magnitude of harms and benefits and risks, can be highly intuitive. We may, for example, all agree that breaking your leg is a harm; I bet there would be pretty good agreement about that. It causes pain, it interferes with normal functioning, et cetera. But then if we turn to this question of, well, how harmful is it? It is a moderate harm? Is it a severe harm? Is it a moderate-to-severe harm? I can't think of any rule, any principle, any set of necessary and sufficient conditions that's going to tell you where on the scale you should rank that. And there hasn't been tons of philosophical work on harm or risk magnitude that I've seen, magnitude specifically, but what's out there, you will find lots of statements sort of agreeing with this.

And more generally, when we talk about prudential value, when it comes to putting specific things on our list of what's valuable or not, you'll find lots of quotes from philosophers writing about this, saying that, you know, reflective intuition seems to be a major determinant in that. There's lots of argument about whether the source of value is pleasure, or the desire, or satisfaction, or something else, but when it comes actually to putting things on our list, intuition plays a big part.

So all of this is to say that if minimal risk means a judgment of risk magnitude, I don’t think we’re going to come up with any determinant definition that also is philosophically plausible at the same time.

Now, the second way to understand minimal risk is as a judgment of acceptable risk, a normative judgment of some kind. And I have a quote here from a recent commentary, by Anna Westra and colleagues, where they basically accuse the current regulatory definition of confusing the descriptive and the normative; that is, confusing what is the case with what ought to be the case. And they say, look, this definition tells us that routine examination risks and daily life risks are acceptable in the context of non-beneficial pediatric research, but we need a reason for thinking they're acceptable, and it doesn’t give us this reason. Why should we think this is the case? You can find other quotes from other commentators in the literature to this effect.

So this just raises the questions, if minimal risk represents some kind of judgment about acceptability, or some sort of justification, in what specific ways are the risk categories normative, and what kind of specification and justification can we reasonably expect? And here I think it’s useful to draw a distinction between sort of a broad, all-things-considered justification of non-beneficial pediatric

research, saying, look, this is what's acceptable, and this is why. Draw a distinction between that and a much more narrow judgment of acceptably low risk.

Strictly speaking, the term "minimal risk" doesn't beg the question in a broad way, as I think Westra and colleagues have accused of it. Once again, if you go back to the Commission's report, minimal risk gets slotted into this considered judgment about the acceptability of low-risk research, even when it's non-beneficial, and there's a whole chapter of ethical discussion leading up to that. So it's not as if this term just fell from the sky, and they just flatly asserted that daily life risk is acceptable, or routine examination risk was acceptable. There's a context for that. Now, people may disagree with the Commission. You may think that maybe that no non-beneficial research is acceptable, or you might word it differently, or maybe you agree with the Commission but disagree with how they got to that conclusion, and we should have those conversations. But minimal risk is not the appropriate place to try to dump all of that normative weight. The term has a very different context and origin, and it's just not conceptually suited to bear that weight.

Now, there's a slightly narrower and I think more plausible way to understand minimal risk as a judgment of acceptable risk, a normative judgment, and that's acceptably low

risk. And you've seen this term bandied about, but what does it mean? So here's my best sense of what it could mean. We start with this general considered judgment that a lot of people share, although certainly not everybody, that non-beneficial pediatric research can be ethically acceptable when the risks are low, and when certain other criteria are satisfied, assent, permission from the parents, et cetera. And then we are presented with a risk or a set of risks that we would be disposed to evaluate as low.

Okay, so we have this set of risks. Let's just say there's 10 before us, and in the abstract, we say, "Oh, these are all low risks, I don't know, 1 in 10,000, you know, probability of hematoma," or whatever you want to put on list. It may be the case that of this group of risks that we are inclined to evaluate as well, some of them we think are acceptable in the context of non-beneficial research, and some we don't. And the way that I make sense of this is by observing that our qualitative judgments about risk magnitude are only going to be able to take us so far. All right? They're very rough. It's highly unlikely we're going to come up with any quantitative scale about risk, so instead, we have to use these kinds of modifiers: low, minimal, moderate, et cetera. And they can only refine things so far.

So we start with this judgment of low, but what we really want is not just low but acceptably low, and looking to the context of the activities in which risks are encountered may help us to make judgments about acceptably low. So this is why I think daily life, or charitable activities, for example, can help us to ballpark this. But, if we turn to the question of, well, can we come up with a definite, you know, definition of acceptably low risk, is there some rule I can come up with, or is there some set of necessary and sufficient conditions that I can throw in the regulations that are going to say when a risk is acceptably low? I doubt it.

There are times in moral reasoning where we can argue from a set of premises to a certain conclusion, and we make use of rules and principles all the time, full-fledged ethical theories, Kantianism, utilitarianism, natural rights theory, et cetera. There's a lot of logic we use in moral argumentation. But, in addition to that, there's also lots of places where we have to fall back on and consider intuition.

Sometimes, this is with very fundamental moral judgments. A lot of people would say, for example, that a principle of nonmaleficence that we shouldn't harm others. There's not really any more fundamental justification you're going to be able to get for that. You can only regress in justification so far, and at that point, you either have to

accept it or not. We also see, consider judgments at the very specific level. I would say that the Commission's considered judgment about the permissibility of low-risk, non-beneficial pediatric research is a considered judgment in the sense that there's lots of stuff they took into account when coming to that conclusion, but you can't say exactly how. So they looked at our obligations of nonmaleficence to children, our special obligations to protect them, the importance of consent, the social importance of pediatric research, and are there alternatives, and what would the world be like if we didn't do it? They looked at all these things, but it's not as though they fed them into a computer, or they fed it into some deductive algorithm that then spit out their conclusion. So the proper way to conceptually frame it is to say that they came to a considered judgment in light of a certain set of considerations, but the exact way that the considerations proves the judgment isn't specifiable.

I suspect that acceptably low risk is just such a judgment. I could be wrong. I've thought about it for a number of years now, and I have some familiarity with philosophical theory, and I can't think of any determinant definition. But maybe somebody will come along and prove me wrong about that.

Okay, a brief note on risk comparison. I'm going to blow through this because Dr. Wendler did a good job. If

minimal risk is indeterminate, then it follows that risk comparisons are going to be indeterminate, too. That is, if we can't say the exactness and precision when a particular risk is minimal, according to some sort of algorithm or set of conditions, then it follows that we're also not going to be able to say, in the same manner, whether one risk is higher or lower than another.

We can go further and we can observe that risk comparison involves a whole host of value judgments. I've got three here. One is the categorization and ranking of harms, and Dr. Wendler talked about this and acknowledged its value judgment. There's also risk equivalence, when we're moving between risks of different harm magnitude. So if risk is a function of probability and harm magnitude, then it follows that a risk of very high harm magnitude with a very low probability could be prudentially or morally equivalent to a risk of lower harm magnitude but higher probability. So there's a value judgment involved in making these kinds of comparisons, and, of course, evidential value judgments. Do we have enough evidence to say that this risk is real, and how do we decide when we have enough evidence? This has been something philosophers of science have talked about a lot. Also, even if we're comparing different risks of the same harm magnitude, what if there's multiple probabilities of the same harm? What do we do with

that? Do we average them? Do we use the highest? Do we use the lowest? There's some augmentation or some auxiliary judgment that has to be made.

So, to my knowledge, SERR is the only comparison framework that's been proposed. I do think it's useful as a heuristic device. Dr. Wendler, in both the paper and his discussion, talked about multiple levels of normative judgment there, so we agree about that. I think I would probably list additional normative judgments over and above what are discussed in that paper, and then the questions is, what do you do about that? And to my mind, yeah, it has its place, but I don't think that we can rely rigidly upon it because I think there's too many dimensions of lability in terms of normative judgments that have to be made, and I don't see any way to specify exactly how they should be made.

Doing okay, 20 minutes. All right. So, the cumulative argument up to this point, which I realize has been very quickly and dirty, and that's just kind of the way it has to be for a short presentation like this, I don't think that if we're after a conceptually defensible understanding of minimal risk, we're going to be able to define it specifically. I just don't think that's possible. And the same thing goes for risk comparison.

So what do we do in light of that? Well, again, one option is we say, well, we should favor a more concrete approach for reasons X, Y, or Z, and acknowledge that it doesn't get it exactly right, but it gets it good enough. But again, I think there's a broader discussion that has to be had about that because the approaches that don't get it good enough are either going to be too restrictive, or they may allow for excessive risk sometimes. The other option is to see if we can do more in a different vein. And so just because I think that risk evaluations are highly intuitive doesn't mean that they are barely intuitive. And there's a different way to look at it. I would suggest, instead of trying to solve this Goldilocks problem, we should concentrate more on making risk evaluations under the appropriate conditions.

And there's two traditions in philosophy I think we can draw on for inspiration here. One is what's called a dispositional or ideal spectator tradition. And this tradition looks at objectivity and moral judgment, not as the result of conforming to some set of rules, but instead, objectivity as a function of making those judgments under the right conditions. And you could say, well, what are the right conditions? Is there anything we could put on that list? I'll give you three here. One is full and relevant information. Dr. Wendler talked about the liabilities of making bare intuitive judgments without

accurate probabilistic information, and I agree with him wholeheartedly on that. Making a risk evaluation with accurate probabilistic information makes for a more defensible evaluation than making it without that information.

Secondly, imaginative acquaintance, or what some philosophers have called omnipercipience. The idea here is that if we're making judgments about risk, and the harm is one part of that risk, if we can accurately understand, or phenomenologically put ourselves in the position of someone having experienced that harm, we can make a more defensible evaluation. Whether we directly have experienced that outcome, or we know somebody who has, or we could talk to somebody who has, it improves the defensibility of the judgment.

And finally, freedom from bias. It is pretty widely acknowledged that there are various sorts of things that can distort or bias our moral judgments. Conflict of interest, financial conflict of interest would be one, but there's all sorts of group affiliation biases and things, too, that do it. And it's better for us to make judgments without those biases than it is for us to make those judgments with them.

Now, note, these are all conditions that improve the defensibility of our risk evaluation, but you can't say exactly how, can you? You just say that it's better if we make them

under these conditions than if we don't. There's no way I can think of to fit them into a framework.

Now the second tradition is what's called a deliberate democratic tradition in political philosophy, which says that defensible public policies are not simply the result of majoritarian vote, but instead must be the product of respectful and reason-giving deliberation, and inclusive deliberation between different parties. And we can appreciate how robust deliberation can improve our risk evaluations. The dispositional model I just sketched, you could do that by yourself sitting in your office alone, as it were. You can reflect on those things, and say, "Well, do I know this, am I being biased," et cetera. But if you have a group of people coming together, it can improve that process, because it's more likely you're going to get relevant empirical information and have that exchange. It's more likely that you're going to have somebody who has some better understanding, perhaps, of what it would be like for a certain harm to transpire, or you can find those people and bring them in. And, of course, since everybody's got their own biases, and the more people you have involved, the more likely you are to uncover them. Or, at the very least, if you don't uncover them, since that can be uncomfortable, to sort of counterbalance them.

So if you stick these two things together, what do you get? You get what I call a dispositional deliberative approach. There's a lot of work that needs to be done to sort of develop this further, and I have a paper that hopefully soon will be out, which starts to do this, but in practice we could beyond this, I think.

Number one, we want a list of appropriate conditions. I've given you three, there could be more, and we could say a lot more about even the three I just mentioned. Secondly, we want appropriate attention to IRB composition, which is something that a number of reports and commentators have talked about in recent years, anyway. For example, we want a greater proportion of non-scientists or non-affiliated members on IRBs, but we can certainly appreciate how, on this model, it's going to be very helpful to expand our deliberation and expand the people who are doing this. And C, we don't have to have this, but it might be helpful to have a procedural algorithm that says this is the order in which you should consider these things. This is, you know, subsidiary points that you want to consider under each bullet point, and this is what you need to resolve before you move on to the next step. But elsewhere, I've started to sketch out what that might look like.

Okay, wow, I'm on my last slide and I've got five minutes. So this brings me to the pragmatic stuff, and I'm just

going to be very brief here. We have pro tanto reasons to start with the most philosophically sound approach, because after all, the whole reason why we have these regulations in the first place is for ethical reasons, right? We want to allow pediatric research because it's important to the development of safe and effective medicines and therapeutics, but all human subjects deserve protection, and children deserve special protection, and we want to try to weave our way as best as possible between those two competing concerns.

So for that reason, it makes sense we want to start with the approach that's most conceptually sound. I happen to think this is that kind of approach. I could be wrong. But then there's the pragmatics. Well, what do you do about, you know, time? What do you about IRB consistency, et cetera.

The one pragmatic objection I'll address briefly is what you could call the "good enough" objection. And that says something like the following. "Well, okay, fine, John, I'll grant you this conceptual argument, but in the real world you've got to deal with pragmatics." And why don't we prefer an approach that gets it close enough and still allows us to, you know, have, you know, added concreteness, et cetera, over this approach. I call it the "good enough" objection because it gets a "Good enough."

Even if you are inclined to this kind of argument, and it may be a sound argument, let’s note that there’s a yardstick you need to have, right? If you’re going to say it’s good enough, that means you need to know what it would be like ideally. By analogy, if I rip a page out of a cookbook, and I want to bake a cake, and I follow the recipe, and I’m looking at the picture, and it comes out, and I'm like, "It doesn’t look like the picture, but it’s good enough," I need to have that picture to tell me what it should be. So what this means is that if we want to go with the "good enough" direction we still need some sort of ideal, and so I would suggest that kind of approach is the best possible thing we’re going to be able to come up with, philosophically, to get us toward that ideal, and only once we have that can we then say, "Okay, it’s good enough," and notice, there will be a normative judgment. How close is good enough?

Secondly, there have been studies that have documented IRB inconsistency; we all know this. To my mind, it’s not clear why. We don’t have a lot of good probabilistic information on the risks we face in daily life. It’s only been in recent years that that’s even been attempted, and there’s still a lot that we don’t have. So when IRBs are coming to different judgments, perhaps that’s for normative reasons. But perhaps also it’s because they don’t have the right empirical information. And if

you gave them more empirical information, you may see more convergence.

Why is that important? Well, it's important because one potential objection to this approach is to say, well, if it's intuitive, even if it's informed intuition, what's going to happen if different IRBs come to different conclusions. To my mind, that's an open empirical question, and we shouldn't beg that question either way. It's entirely possible that if we were to implement this model in a robust way, and have the appropriate empirical information, and also pay attention to the other moral concerns I've outlined, you might see a pretty good divergence in IRB judgments. And on top of that, there's other ways you might try to resolve differences between IRBs. And furthermore, if we don't have that empirical information, then this approach is no worse than even trying to implement a daily life standard because you can't implement it if you don't have the empirical information, which is why you're seeing the variability.

So that's just one pragmatic objection; there's potentially others I can address, but I'm going to stop there. I appreciate your attention. Are we doing questions, or just moving on to the next?

CHAIRMAN BOTKIN: Well, Dr. Rossi, thank you very much. Fascinating presentation. Unfortunately, due to time

constraints, and due to the time constraints for our next speaker, I’m afraid we’re going to have to forego a question period here, and move on to Dr. Susan Coller-Monarez. Hopefully I've got that pronunciation there reasonably right. She's going to be speaking to us about Using Risk to Inform Biodefense Decision Making.

What's the correct pronunciation?

DR. COLLER-MONAREZ: Monarez.

CHAIRMAN BOTKIN: Monarez. All right. So Dr. Susan Coller-Monarez is the Chief of the Threat Characterization and Attribution Branch within the Department of Homeland Security. Dr. Coller-Monarez oversees the Department of Homeland Security's chemical, biological, radiological, and nuclear risk assessments, microbial forensics, and bio-threat characterization programs. Prior to her current position, she served as a Policy Analyst at the Department of Health and Human Services within the Office of the Assistant Secretary of Preparedness and Response. And prior to government service, she served as a successful research scientist in the field of immunology and infectious diseases. So, welcome.

DR. COLLER-MONAREZ: Thank you. So what I'm going to plan on doing is actually hit some of the highlights associated with my presentation, and I won't go into the level of technical depth that are reflected in my slides. You have my slides. And I will try to get this briefing in about 10 or 15 minutes, and leave a little bit of rooms for questions, should they arise. But also make myself available if there's any follow-on questions. Unfortunately, I do need to leave to get back out downtown for a meeting, but I talked to Skip, and I'm certainly willing to meet with you individually or as a group at a subsequent time over the course of your deliberations and this

discussion to provide any information that I can relevant and associated with our risk assessments.

Okay, so the goal is for DHS to the risk assessments that are used both internally in the DHS to inform our own programs, as well as our interagency partners across the Homeland Security Enterprise. And so really what happened is, in 2001, we had the Amerithrax attacks. And then there was some conscious effort made amongst those in government at the time to try to assemble a baseline understanding of risk that could be used to then inform many aspects that will come into play in CBRN defense.

And so in 2004, there was a White House Presidential directive that came out and gave the DHS the mandate to work with our interagency partners to come up with a defensible risk assessment to help inform everything from infrastructure protection, event detection, medical countermeasure development, and decontamination strategies. And really look at what areas need to be prioritized based on the agents of concern, and then the potential targets. And so since that time, DHS has been developing a risk assessment capability. It’s undergone some evolution since its origin, and we’re now in a position where the information that is integrated and extractable from our risk assessments is becoming quite valuable in informing decision making across the government.

Okay, so I think we've heard a lot about why one would use risk assessments, specifically in terms of biodefense, chemical defense. The frequency and the severity associated with any scenarios that one has to consider are going to play a very important role in how one attempts to mitigate the effects associated with that event. The risk assessments as we've developed them will allow us to answer the questions of, what are we worried about? Do we put all of our efforts associated with a specific agent? With multiple agents? And how does one prioritize those? How likely is it? Is this something that would happen on an every-year basis? Every five years, 10 years, every thousand years? What targets, essentially, are we looking at? What is the magnitude? How bad could it be? Are we talking about a population of five or more exposed, or are we talking about a hundred, tens of hundreds, hundreds of thousands to be exposed. And then one of the things that we're able to do within our risk assessments is go back and re-interrogate what are the factors associated with the risk? So I'll get to the elements that comprise our risk assessments in a few slides, but when I talk about why we chose the approach that we chose, it was really so that we actually could go back in and do that interrogation and look at those elements.

The strength in having a common risk assessment that is provided to our Homeland Security partners is that it gives

us a common framework to look at what are the mitigation methods that can be applied? What can be done? And then to what extent are these impactful in reducing the consequence associated with any of the attacks that might occur?

Okay, so you've heard a lot about there are a variety of different risk assessments, approached that can be used. We, at DHS, evaluated many of these at a high level. We looked at everything from just, you know, the sort of actuarial risk assessment, where you take historical data and you try to apply it looking at potential future outcomes. There's qualitative risk assessments, which is essentially where you sit around with subject matter experts, and you may apply some sort of a formalized process in place, but at the end of the day, it is largely driven by subject matter expert opinion.

What we ultimately decide to do within DHS is use a quantitative risk assessment. And what that allows us to do is take both the opinion of the subject matter experts, integrate it with the intelligence/threat information, plus the empirical evidence associated with the specific characteristics of any of the agents, the targets, and then the mitigation steps. And it allows us to then have a more unbiased approach to the risk that's also translatable over time. So you will apply the same methodological approach. The threat side gets updated on a periodic basis. The understanding about production or

dissemination capabilities of many of the agents is updated. But you have the same approach year after year after year, and so there is some way to go back and to evaluate what has changed and why it's changed.

I'm going to skip this, but essentially what PRA is, you apply probabilities associated with any of the events. So there are two components to our risk assessments. There's the probability component, where we look at how likely is something to happen. And then there's the consequence, is, given that likelihood, what are the potential outcomes. And so in our risk assessments, we evaluate three types of actuary groups. We look at those that are minimally technically inclined or minimally resourced. We look at those who have some moderate capabilities. And then we look at those potential adversaries that have some higher skill set and greater access to materials and resources.

And then what we do is we look at potential targets. So this is everything from the very high level, indoors, outdoors, food, water, subways, to more specific targets, where we look at within the indoor environment subsets, arenas, federal buildings, those sorts of things. And so there are 26 different targets types that we evaluate within our risk assessment.

We look at a wide variety of agents. So for our integrated risk assessment, which looks across CBRN, we have 153 agents that are taken into consideration. For our biospecific risk assessment, we look on the order of about 40 different agents and accumulate the characteristics associated with those.

I'll run through a quick scenario so that you understand how we formulate the consequences. For example, if we took a low-resourced adversary who chose a particular biological agent, understanding the production and dissemination characteristics associated with that agent, one could imagine it would disseminate in a certain way and affect a target population which is modeled within that target type. And so given the amount exposed, and the amount produced, the dissemination mechanism, the amount of material that would be presented to that particular target, the individual in that target, they would be expected to have a certain number of individuals who would receive an LD50 of that particular agent. Given that, there is an expectation that, you know, a certain number of them would benefit from mitigation given at certain periods of times post-exposure. And so altogether, those elements are put in, and what you end up with is the relative risk, both associated with a particular agent, with a particular target, and then the consequences associated with that.

Okay, so I'm going to go through this very quickly. Essentially, this is in your packet. These are the examples, if you want to look at an event tree, different organizations, different agents, selected targets, and then the mechanism of acquisition and deployment, essentially what I've talked about.

Okay, so I want to talk a little bit about this to give you some more sense about all of the inputs into our model. When I have an opportunity to talk about risk assessment, one of the biggest questions is, "Okay, we get that you do can do this; how do you do this?" And I apologize, we don't have time to go through this in exquisite detail, but essentially we have various models that take the information, and I'm not a computer scientist, I'm an immunologist, so I will not pretend to understand how one codes in for the different decision making. But I will tell you that on the verification/validation side, what we can do is actually make sure that the computer scientists who are taking that information are developing outputs that are consistent with our expectation. So, essentially, we have a production model. So that means we look at how one might produce a particular agent, and the inherent stability of it, and how long it should be stored, and how much that is produced would actually be viable for dissemination.

We have a respirable fraction calculation, and so that essentially looks at when one disseminates through a variety of

different technical tools, there is going to be a loss associated with that, with virtually every type of biological organism, just due to sharing factors, and when an agent were to dry down, and long-term viability. We have models associated with indoor inhalation, outdoor inhalation, contact, and subway. And so there are very specific aspects associated with each one of these target types, in terms of the impact of the agent, how it moves, how people move. We have water and food ingestion models, and those are based on, you know, again, agent stability in those different forum.

And then we look at index infections, the human vector: so these are really only critical for those agents that are expected to have some transmissibility. So that's, as you know, that's a limited number of the agents. This is moved into our public health response model, which I'll get to you in a little more detail in the next slide. And the outcomes are both the illness and fatalities, and then we also have some economic modeling that will help one understand the economic impact should an event take place.

So the public health model, and I should say, this is something that we do, actually, in very close coordination with our colleagues at HHS. So BARDA has a quite advanced modeling capability, and so I work quite closely with Dr. Tim Lant, who is the director of their BARDA modeling. And this is one of the

products that they actually work hand-in-hand with us and is vetted through their subject matter experts as well as those here at FDA, and CDC, and NIH, to make sure that it's well informed by public health. And what we know about these diseases to the extent that we have information that can be correlated.

So you have a total population, and you have susceptible population that is then exposed to the certain material. People can then either become incubating if they are exposed to enough of the material that it would actually potentially cause illness, and then you also have integrated into our model in terms of helping bound the public health response those who may have been in the proximity of the release, but who are themselves not actually exposed.

So then people moving from incubating to ill, but not seeking care; ill who seek care; and then those who are provided a post-exposure prophylactic. So of those three categories, there is a certain percentage that will move towards those who had received a large enough dose that it's a fatality. They become dead. There are those who seek care, or were exposed to a lower amount of the material, that recover, and then there are those who were never exposed in the first place, and who just transit through the model as part of the worried well.

So the outputs that we have with our risk assessment are very superficial, and I should say that the outputs that we have can be ordinarily detailed, or they could be very high-level. And what I've just giving you are notional results, which, essentially, when one looks at a high level, one can extract information such as, should we worry on a percentile basis more about Agent A versus Agent B versus Agent C? And that's in terms of probability times those consequences. So that gives you a high level. We don't have to worry about agents, you know, X + 23. Because that agent is really so far down on our probability and consequences standpoint that it's better to focus on those agents that pose the greatest risk.

And then we also have the ability to break out by target, which becomes quite important when one is looking at infrastructure protection, or response capabilities, or population movement, trying to get people out of a contaminated area, we can say. There are some agents that pose a significant risk in certain venues, and then there are some agents that do not pose a significant risk in some venues. And so it's important to have that in mind when one is thinking about whether a large outdoor release is going to be required for planning for all agents. Or whether in some targets which will restrict a number of people who may be exposed, those are the agents that are a higher priority. And so it just gives you the

ability to really interrogate the data in a way that can be meaningful when one is actually attempting to develop a post-event response capability.

So one of the things that we are now using our risk assessments, too, is actually develop very specific scenarios to help planning efforts. And so we're working with our colleagues across the interagency. And what we do is take in the outputs, which are largely driven by probability and consequences. And you can look across the entire risk space and narrow down on those areas that are of greatest interest to you as you're planning your mitigation efforts. And so you can actually look and bound your discussion by a scenario that would be in the highest risk space, and say, "We're worried about this agent on this target that has the potential to have this amount of consequences." And it really helps when one is trying to get a common sort of baseline for what we're talking about. I think the challenge in biodefense, and at least what I faced initially when I was over at HHS in BARDA, was trying to make sure that we all had in mind, when we were thinking about the scenario that we're planning for, the common scenario, so that we all are working from the same initiation point.

So, again, this is in your handouts. We have a variety of partners that we're currently working with, that we're using our risk assessments to support their planning. The

majority of it is in the classified space, although we are working very diligently to try to take some of our results and modify them in such a way that they can be used in the FOU or potentially unclassified venues. And that's something that we're hoping in the next year or so that we'll actually begin to push more of that out. But right now, most of it is within that classified realm.

Okay, so, just a summary, as I said we work with our partners to make sure that this information, as a common baseline, is made available to their efforts, and I'm happy to take any questions.

CHAIRMAN BOTKIN: Thank you. We do have time for some questions.

DR. GLANTZ: What I didn't see in the model was the probability or likelihood that something would actually happen. I mean, it looks like, if it happens, someone like Herman Kahn during the nuclear area. Like if there's nuclear war, here's how many people will die. But there was no estimate of the chances of there being a nuclear war.

DR. COLLER-MONAREZ: Right.

DR. DAUM: I can see that here.

DR. COLLER-MONAREZ: Right. So, the question is, is this compared to it not happening? And there are other analyses that Homeland Security does do that look across all risks that

are presented to the population, hurricanes, earthquakes, traffic accidents, all those sorts of things, and tries to rack and stack CBRN events against those. Our supposition when doing our risk assessments is that it will happen. Right? So, we're not trying to rack it and stack it against not happening. It's presupposing that should there be a biological attack using an agent that we assume will have clinical relevance to a susceptible population, what are the chances of that against its counterparts, would that happen.

DR. GLANTZ: You lost me at the very end of that. So are you saying that you don't deal with the issue of what are the chances of it happening?

DR. COLLER-MONAREZ: That's right.

DR. GLANTZ: But that if it happened, here's how you would respond.

DR. COLLER-MONAREZ: The results of our analysis are assuming that it will happen.

DR. GLANTZ: Assuming it will happen.

DR. COLLER-MONAREZ: Yes.

CHAIRMAN BOTKIN: Skip?

DR. NELSON: Just a question, given the opportunity to talk about something that we've talked about is, on the possibility that there was a protocol that came forward for 50/50 full review, where some of this information about risk was

considered relevant to that protocol, I'm just curious what your thoughts are about what could or couldn't be shared in what would then be a sort of public discussion.

DR. COLLER-MONAREZ: Yeah, so it's a good question. I don't know the extent of the deliberations that you are going to have. I mean, this is something that, as I understand it, will be further deliberated over the next day or so. My recommendation, and what we had talked about, is that to help understand the risk-benefit equation, it would be worthwhile for those of you who are in a position to desire and have the opportunity to get a more sensitive briefing associated with the results that are coming out of our assessment, I think it would be beneficial to talk about that as you consider the path forward in the pediatric population and medical countermeasure development.

At this time, we wouldn't have the ability to provide that level of sensitive information in a public forum because it is driven by our work with the intelligence community and it has threat information, and it would reveal, essentially, vulnerabilities if we were to provide it. So, in that regard, I would suggest that it would be in a different forum.

CHAIRMAN BOTKIN: Dr. Bradley.

DR. BRADLEY: Thank you very much for that presentation. Steve Krug and I are on the NBSB team, and we had

the pleasure of Dr. Lant's presentation on modeling, and we are worried. And as Skip and I talked about almost two years ago, the issue of whether you proceed with a minimal or minor over minimal risk research is largely based on your risk assessment; that is difficult to share. And Dr. Lant even said that even said the Dark Zephyr exercise of anthrax on San Francisco, he said that's not publicly available, only based on the need to know.

So I agree with Skip, the more information we have, the better judgment we can make on whether certain minimal or minor above minimal risks are justified. And then there's the, and I hate to use the word "political," but when Tim says there's a 2 percent risk, is that a high enough risk to be worth doing research on? And there's a political public spin on whether that risk is acceptable. So even if you could define the risk with variability, there is a political overlay on whether that risk is worth taking that needs to be discussed. And this is a great ethics community to do that. Thank you.

CHAIRMAN BOTKIN: Dr. Joffe.

DR. JOFFE: Steve Joffe. My question follows up on Professor Glantz's question. So if your risk assessments don't incorporate the judgments about the probability that an event will happen in the first place, is somebody else making those risk assessments, and would that be a part of any decision-

making process, because it’s very difficult for me to imagine how one might think through this problem without estimates of that sort of critical information.

DR. COLLER-MONAREZ: All right, so I guess I should clarify when I say that the risk is assumed that it will happen, that's not an indicator of the frequency by which it would happen. So that is incorporated within our risk assessment. So, again, in a different venue, we could talk about the potential frequency with which one would use a particular agent and a particular target, and a certain population would be impacted. So what I can tell you is that you were able to see the analysis, you could say, “Okay, what is the frequency that we expect a particular agent to be used in a metro system,” right? And the outcome may be something like one every thousand years. And you could look at that and say, “Okay, how does that change my understanding of, what do I worry about in subway systems?” So the frequency of initiation and that particular scenario is one of the outputs that can be derived from the risk assessment. What would be something that you would have to deliberate is how would you use that to inform your decision making? If it were 1 in 1,000 years, one in 10,000 years, or those sorts of things, how would that alter your thinking? But that’s certainly something that would be something you would want, that you would discuss given your particular mission.

CHAIRMAN BOTKIN: Dr. Krug?

DR. KRUG: Yeah. Thank you, that was a great presentation. Again, I don't have security clearance, or if I do, I haven't been informed. An assessment of risk can be inferred by what little we are aware of in terms of exercises that are being done and by what's in the stockpile. So there's a lot of anthrax vaccine in the stockpile, I can't tell you exactly how much because I don't know.

[laughter]

And that's been developed based upon informed individuals' knowledge about the consequences of disease, and the likelihood, even small, that that could happen. The dilemma that we have, the dilemma that the Presidential Commission has, is that it's difficult to go through the exercise of understanding the risk-benefit ratio. In the pediatric population, where there should be a higher standard, absolutely. Yet, we can't come to grips with the risk of disease. We can all read about anthrax, and it's pretty darn scary, and if you want to have your pants scared off, have some people show you their exercise. But that's the dilemma that we have. And the process, as I am understanding it, is that if we ever use the escape hatch, that's going to require, first of all, another focus group looking at the proposal, but also transparency and public comment. So how do you achieve that? How do we open the

door enough so that we can at least inform the public that this is not some plot that somebody's making up somewhere, but, in fact, the risk real. We have to, at some point in time, be able to do that otherwise the point is moot here.

DR. COLLER-MONAREZ: Yes, it's an extraordinarily challenging position that you are in, I will say. It's more so than I would submit many of our partners are, because what you do has to be made public, largely to get buy-in by anyone who would potentially want to either volunteer to be in a trial or ultimately use the product. It's a unique position. And I don't know that I have the answer in terms of how we can translate this sensitive risk information into something that would be defensible in your collective groups' minds to be able to articulate to a public. That might be something that if we had a different forum, a different conversation, that we could iterate on.

CHAIRMAN BOTKIN: Dr. Kopelman?

DR. KOPELMAN: Thank you, my assistant. [laughs] Loretta Kopelman. Help me to understand: When you take a child into an emergency department because he's severely harmed, all usual rules about consent are waived, and you just take care of the child. Yet here, it seems you're trying to take a picture of substantial risk to children, and fit it into the usual, everyday rules of the four levels of risk assessment for

children's research. If the risk is that substantial, why are you trying to fit it into normal research regulations?

DR. COLLER-MONAREZ: So, specifically with the pediatric population, I wouldn't, and I hope I haven't inappropriately conveyed that there is a difference in the risk associated with anyone in the pediatric population than in the normal population. That would certainly need to be something that was in a different forum. I think that in terms of the mission that you're under, it's more of the, is there something special about a pediatric case that would occur in the context of the rest of the event that would warrant the motivation for wanting to have a medical countermeasure available specifically to attend to them would be at a higher level than wanting to have your normal population protected. But that's something that the Pediatrics Ethics Commission would have to discuss, and it's not something that's risk assessment can tell you specifically, at least in this forum.

DR. KOPELMAN: But if you can't fulfill the highest level, if you can't fulfill the duty for public comment and all information a reasonable person would want, then are you really using these guidelines?

DR. COLLER-MONAREZ: I don't know if that's a question for me, I think that's a question for this organization, or this group. As a purveyor of the risk assessment, what I can give

you is the information associated with who might be in a target that an adversary would choose to deploy a biological weapon. And what might they be exposed to in terms of, would they cause enough severe illness that they would need treatment that would either approved or under some sort of EUA under this process.

CHAIRMAN BOTKIN: Skip, did you want to respond directly to that?

DR. NELSON: No, I just want to point out that that's the second half of Question 3, which is precisely what you're talking about, so, I mean, there'll be plenty of time to ponder how and to what degree that information would be available if such a protocol came forward. That's the second part of Question 3.

CHAIRMAN BOTKIN: All right. I think quickly to end up here, Dr. Joffe and Dr. Fost.

DR. JOFFE: So my comment is not directed at you in any way, but I just want to put something on the table that I've heard muttered and that is, I think, implicit in this conversation or in the background of this conversation. Which is, over the last 10 or 12 years, episodes of being assured at the public level about risks based upon classified information that turned out not to be the case.

And so that's a level of, I think, justified skepticism on the part of the public, on the part of people who

must make decisions based upon classified information. So not only is it sort of generically difficult to make decisions based upon information that's not entirely public, but in the sort of context of the recent past, and episodes of being assured about information that was classified that was not generally available that turned out not to be justified and used for purposes of the sort of lead decision makers, I think that's just an important background fact that certainly is in my mind as we think through decisions that must be made on the basis of information that we can't all have access to.

DR. FOST: Norm Fost. I asked earlier, why are we here, since it sounds like, at least with regard to countermeasures, there are ample mechanisms for getting needed drugs and so on out there. But in thinking about the answer to Loretta's question, I think I finally get why we're here, and so I'm just going to say it; it's for somebody to correct me or confirm so I understand what the project is.

If there is really an attack, or a very high risk of an attack, then there's a clear prospect of benefit for children of all ages to get products or to be in trials that can be rapidly done because if there's a very high risk of something bad happening to them, there's a prospect of direct benefit. I think why we're here, and this is my evolving sense of it, is since we can't know that, and we're not going to know that,

given the information is either classified or unknowable, the question that's being asked is: what if there's no prospect of an attack? And so we can't posit any potential benefit for children. What kind of studies could be done under those circumstances, where there's no pretense of any benefit because we're just stipulating that it's zero. And to do that kind of research, it has meet the minimal risk requirement. So in this absence of any real threat or known threat, what kind of minimal risk research can be done? That's my sense of why we're here.

CHAIRMAN BOTKIN: Do you have something quick, Dr. Wilfond?

DR. WILFOND: Yeah, I can make it really quick, it's really a response to both Steve, and partially to Norm. I really think we're overemphasizing the likelihood of an event. I mean, I think whether we're talking about a terrorist attack, or whether we're talking about a massive hurricane that wipes out a city, it's a possibility, it's not impossible. And I think that's all we need to know to ask the questions right before us today.

DR. COLLER-MONAREZ: Can I just make one more statement? I think that's exactly correct. If it were me who were sitting at the table, I think what I would do is probably try to identify all of those things that could be done that would pose a minimal risk to those who would be involved in the

types, or studies, or analysis. But I'd go one step further and outline what are those things that would have to be done rapidly if the risk was moved from where it is to something that's more imminent, right? Let's say a week from now, or two weeks from now, or two years from now, there was an indication that something was much more likely to happen. And so that you would have the ability, the agility, under those circumstances, to rapidly go from this body of information that would be established today to being able to take the next step, depending on what your risk-benefit analysis turns out in terms of the pediatric population, where you would accept a higher level of risk associated with that population.

But what I would do, as you're outlining that, is try to identify how you would integrate yourselves with the Homeland Security community with the risk assessments to make sure that there is some integration so that you would be aware when things changed from the current status to something different. That would just be my recommendation.

CHAIRMAN BOTKIN: All right, thank you very much. We're going to break for lunch now. We originally had 12:00 to 1:00 for lunch. It's now 12:40. So I don't quite know how efficient the lunch services are here, but I would like to reconvene at 12:20. I'm sorry, at 1:20, if we could do so. So let's plan on reconvening at about 40 minutes. My understanding

is, just for general information, is that there’s a buffet at the restaurant that's within the hotel. A number of other restaurants might be in the vicinity.

DR. ELLENBERG: And I’d also remind everybody, this is Walt Ellenberg, I’d like to remind everybody at the committee table to please refrain from outside discussion while you are not in this meeting room. Thank you.

[Break]

PROBABILISTIC MODELS OF RISK: PEDIATRIC RESEARCH PROTOCOLS INVOLVING MEDICAL COUNTERMEASURES

CHAIRMAN BOTKIN: Okay. Let's go ahead and get started. All right, our next speaker, Dr. Dan Fagbuyi, hopefully that's a reasonably correct pronunciation. He's going to speak with us about Probabilistic Models of Risk: Pediatric Research Protocols involving Medical Countermeasures. Dr. Fagbuyi is the Medical Director of Disaster Preparedness and Emergency Management at Children's National Medical Center here in Washington, providing strategic leadership and disaster preparedness in response to business continuity and community outreach efforts; Assistant Professor of Pediatrics and Emergency Medicine at the George Washington University School of Medicine; board certification in both pediatrics and pediatric emergency medicine. He was recently appointed to the U.S. Secretary of Health and Human Services by Kathleen Sebelius to the National Biodefense Science Board to provide expert advice and guidance on preventing, preparing for, and defining adverse health consequences in public health emergencies. Dr. Fagbuyi, welcome.

DR. FAGBUYI: Thank you. Good morning. Can everybody hear me in the back? Yes, I know we just ate lunch.

FEMALE SPEAKER: Yes.

DR. FAGBUYI: I'm more of an interactive guy, and my military background makes me sometimes dictatorial, so I apologize for that.

[laughter]

All right. Well, good afternoon. Thank you to FDA, other agencies that are here, my colleagues at the table, this committee for organizing, Skip and the team that's helped them also.

My talk briefly, I know we just ate, so trying to stay awake. Most of my colleagues who have gone before me have actually highlighted some of these things. So I won't rush through the slides, but there'll be some things that may be the same. But I think it's good because it brings everything back into perspective and some of the questions while we were tackling "why are we really here."

So, as I usually do when I give a talk or lecture like this, make sure we have some objectives that we have to meet. So we're going to define risk -- some of my colleagues have already done that -- harm, and benefit. We'll talk about the definition of condition, risk disorder. I think the IOM did a great job in their recommendation in seeing how relevant this is to this discussion. And we'll also try and talk about some of the key concepts and concerns that surround the issue of pediatric medical countermeasures specifically, especially if

there's no prospect of benefit. And that may be subject to definition, because I believe there actually is some benefit. And we'll talk about that as we go on.

Some of the context that we've heard today, and I put these on, these are just buzzwords, and we're going to go into them, but some of my partners have talked about them: minor increase over minimal risk; the fact that there's no prospect of benefit; the issue of disorder versus condition. And what about commensurate experience? Is this of vital importance? These are some of the buzzwords that make us move in a certain direction.

And knowable versus unknowable risks, especially when something's classified, bet you there's all indirect evidence to say that this is obviously something serious to the U.S. government, so therefore, is that implication enough for us to say there is an issue here that we need to address.

So what is risk? It's a complex topic to define. You could use the Webster's dictionary or anything, but risk is very complex. And it's considered, basically, a potential event or some type of action that leads to harm. It's usually characterized by probability, so the likelihood that something's going to happen. And I'll interject some examples in no main order. But there's a likelihood that if I step outside, I can be hit by a car. There's the likelihood that I might fall along

at the podium. There's a likelihood that an attack can occur on our soil, and actually, in fact, some of those things have happened.

So what is that risk? Is there a numeric value that needs to be ascribed to that? How severe is it? What is the impact? As an emergency physician, I'm thinking of what's the impact on the child, not just at age 1, 2, or 3. But I'm thinking 18 years down the line, so this patient is an adult in my eyes. Does that mean this patient is losing a limb, losing eyesight? Does this mean that this patient is going to have chronic disability? Or is it lethal, such as what we're seeing that's going on over in Syria? And is this something related to sarin gas? And that leads to death in a patient. And that's a long-term thing. That means they're no longer breathing.

What about the duration of that? Is it just chronic issues that they'll have to deal with, medical issues long term? Or is it something just temporary, like the stuff some of my colleagues alluded to blood draws, just a stick and a cry, is that reasonable enough, or if it results in debilitative disease, is that something we have to consider.

So minimal risk, they've talked about that, so I'm not going to redefine that. Sounds like there's no real good definition for it. I remember the first time when I came across this definition, I said, "Okay, kids get vaccines all the time,

so if there’s a vaccine that’s being discussed that you've use, it's a vaccine. They get shots all the time, right? So that’s not minimal risk if they get a vaccine that we think is going to save their lives." But this definition is very broad and encompasses a lot of things as they’ve talked about.

So what is harm? Some type of hurtful outcome or actually that occurs? And how do we define that? Is that something that’s just short-lived? Is it something that’s permanent? Is it something that happens early on in the process of developing or doing some research on a medical countermeasure, just, again, using the blood draw as an example? Or is it something that occurs later on, like years down the line, that we find out, "Oh, by the way, this leads to osteomyelitis, an infection in the bone." We find this all the time. You can watch TV and you can see these ads. They say, “If you were exposed to this and this and this, call a lawyer, X, Y, and Z.” And we, in the medical community, kind of cringe with that.

And then the other thing with regard to harm, it can be psychological. Is it just that it causes scarring in the child later on, emotionally, to the point where they are now scared of if they go into enclosed spaces all the time, or for a certain procedure,? Does it ostracize the kid socially from other kids or from other people? Those are some of the things

we have to really grapple with. And then what are potential harms, other potential harms? Even separation of the child from their parents, fear during a process can be a harm that we should consider. And that happens day in and day out in the emergency department when we're seeing patients. Sometimes the parents can't stomach their child crying, or the procedure is something we don't want the parents to watch so we ask them to step out the room. Those are some of the things that we should consider. So these are things that happen in our daily lives and in practice. So when you're defining that minimal risk, you should consider those, and see how broad and how it relates, depending on the setting.

What about benefit? Is there some potential value, some outcome? Or is there an uncertain outcome? We don't know. An incident occurs now. We do some studies. We evaluate certain patients. It gives us some information on maybe what accurate dose we should use in a patient that gives me, as an emergency physician, some type of information that I can actually tell the parents when they come to me and say, "Well, why are we getting this again?" And I would be able, or any of my colleagues would be able, to look them in the eye and say, "Well, we're doing this because X, Y, and Z. Oh, yes, it may cause some swelling and redness on the arm. And they may do

this and that." That's important. But we need to know what that outcome is. Or do we? That's a big question.

And then the issue of magnitude -- some people talked about this -- and the probability and duration; those are other dimensions that we really need to characterize.

I think there's some things that have been talked about, which relate to the issue of geography, and I want to talk about that also.

So, minor over minimal risk. When I read some information about this, it was very puzzling. I said, "So how do you define minor over minimal risk and that gray area?" It still baffles me, and I'm no ethicist, I'm just an emergency department physician who cares about patients who've been dealing with pediatrics for a while. But it still seems like it's a moving target, at least for me. And that's why, I guess, I'm here to see what this wonderful body of knowledge comes up with as their definition.

But this is the true, true definition. And I highlight, in yellow, the buzzwords and the concepts that we need to consider that I talked about earlier. And so for studies that aren't approved under 50.53, and may be approved by HHS Secretary or the FDA Commissioner, those are important things to consider. There may be some potential benefit to kids

in the future, and it may not be to patients who are actually involved in the research.

From one of the exercises we talked about Dark Zephyr earlier which was an exercise that looked at the incident of the response to an anthrax attack in certain geographic area of the nation, and what that would look like. There's some important information that was gleaned from that. And when you consider something that's actually happened in a certain area, for example, in Washington, D.C. here, where we had an anthrax incident, and where we've had even sometimes, periodically, white powder showing up at some public schools, and everybody's in frenzy, it begs the question.

So it has happened before. It can happen. There is a possibility. Is that a risk? The geographic area, is that a risk? Is it just the metropolitan areas that we need to be worried about? I think Dr. Grabenstein brought that up, and I think that's an important issue.

Does that change the dynamic of the risk in that area? If there's something that you know, there's soft targets in a certain area, that's where they're going to go. Is there risk in that area? And I think my argument would be that changes the game. The fact that it's happened and can occur here, that puts us at risk.

So I wanted to talk about disorder versus condition, and really look at that from the perspective of a narrow definition or a broad definition. And I like the broad definition, because if you just define it narrowly, you're talking about illness, injury, or some type of disease process. But broadly, you're talking to a different socioeconomic group, a certain neighborhood that's at risk, presumably a metropolitan area, geographic area, you could be referring to a developmental phase. And I'll talk about this a little bit later.

But when you look at research in a 15- or 16-year-old that we may want to administer a vaccine or draw a specimen on, compare that to maybe an 8-year-old, a 9-year-old. And also, with regards to explaining what that procedure would be like, there's a big difference. There's a difference developmentally and how they understand that. And there's some point at which you can say maybe a 15-, 16-year-old are somewhat similar. And when you categorize patients, maybe that's a better way of looking at it, especially in a setting of medical countermeasures and research that may involve biologics or certain types of therapeutic agents.

So the IOM came up with a set of recommendations. And I love their definition that they used here because it's broad enough to cover what I would say is appropriate as a definition for a condition. And I think the use of "condition" should be

adopted. I'm not going to read it to you, but you probably heard about it, or saw it, or read the report. But it's a great report. I learned a lot, actually, from the documents, that was what I read also in the background of my discussion.

So what are the next steps? Really, where are we going? And how do we actually advance pediatric medical countermeasure research that may be some minor increase over minimal risk?

Well, I think the first thing is that this issue is broader than just a childhood disease. So use the context of influenza, or even the context of some type of intentional agent, where there may not be a disease in a patient, but they are at risk of getting that. We really need to consider that. And if we're not going to use a broader definition, we really need to look at the risk impact, meaning over their lifespan. Are we looking at life years saved versus lives saved? And we need to consider that concept. And what's the magnitude? How big is it? Does it affect the whole population? Does it affect the population in the metropolitan areas? Does it affect the rural area that has less than its population? And where does it occur? Is it in school? Where's the setting? Those are some of the things we really need to factor in into our new definition.

Is it just research that's scientifically necessary? I really don't think it's just because it's scientifically necessary. While that may be a reason, that doesn't justify the process. I think we need to inform our families and from an end-user standpoint, and a person who is dealing with the end-user, I would like to be informed as best as I can, especially in this day and age where we have the science and technology and the capability, we owe it to ourselves, we owe it to our patients to be able to educate them, and also to be able to provide enough data and information on what those risks are and the safety and efficacy of certain interventions. We cannot say we don't have data and we were stuck on getting data because we weren't able to assess this risk or we didn't have as much evidence. That's not going to suffice for the American public, at least in my opinion.

We need to consider redefining MCM research, not only to include potential risk. So it's not just anthrax or some release of a gas, or a sarin, or some type of nerve agent. But also emerging infectious disease threats and SARS is also some type of avian flu or influenza, those types of things we need to consider. And I think in some of the other deliberations on some other ethical committees, those were limited to intentional threats, and I think we need to think broader than that.

The at-risk group, I think we need to also consider not only location but precedent, has this happened before? Has it happened in another nation? What's going on in Syria? Could it happen here? You should ask yourself. It could. That's my opinion. And what's the risk, and which population are affected? And what are the factors? Those are all the things we need to consider.

What about group characteristics? Does that warrant exposure? I think it actually may. The pediatric population, especially the younger crowd, the ones who can't really fend for themselves, this is my job to advocate for them. And we have evidence to know that certain agents have a threat to children, and have a significant threat to their life, meaning extremely lethal. So that characteristic of their vulnerability, I think, needs to be evaluated, makes them move up top of the list.

And how do we get there? So talked about certain characteristics under that condition. So, age de-escalation may be one of the ways we might be able to get there. So it's time to consider, okay, well, we issued you this, and it's a normal routine for those who develop vaccines, where they say certain age groups, they categorize them. And I think that's something we need to start considering, especially when it comes to medical countermeasures also.

That's pretty much my talk. It's really a time for us to think and ponder. And as we dive into the discussion, I just want to make sure we brought those issues up. That's all I have.

CHAIRMAN BOTKIN: Dr. Fagbuyi, thank you. Questions from the group? Dr. Krug?

DR. KRUG: It may be a question, may be a comment. Dan, thank you. I agree with you. And I think that, and we've discussed this here in the morning session, the framework here is a little different; it might require presumably uncertain risk of disease, kind of a different framework. You know, it's clear to me that the FDA has been very creative, and scientifically so, in identifying, and we're distilling data to support, and dosing recommendations from animals to humans and from adult humans to smaller humans. And even also in getting us sort of pre-prepared to do things in terms of pre-event EUAs and INDs.

To the issue at hand, with this particular vaccine, or any vaccine where there's no data, I think of the effects that are for a disease that we've not yet even seen. Little to no data of any kind in children, plus no data on the efficacy of post-exposure prophylaxis, that's the reason why there's not data. Makes complete sense.

We've been talking a lot about risk. And, again, I would wager a dollar at least that we won't figure that out. What about the benefits? Maybe we ought to be looking at this from the other side of the equation. Benefits would afford us to maybe understand the following things. First of all, does this work? Does it work in 40 days? Does it work in 60 days, which is what we expect? Does it work in 80 days?

If, tomorrow, Dark Zephyr happens somewhere, in actuality, knowing that would be really important because there would be lives at stake. To get a child or even an adult to take medication for 60 days in a row, a small miracle needs to occur. And that's with a palatable medication. We're not going to discuss palatability today. And knowing, God forbid, it's 75 days, well, if we're going to stop antibiotics in 60 days, somebody loses there.

The other issue, and again, I think this has come out in a lot of ways, that there's concerns for real interesting barriers because even though the FDA has, again, done masterful work, along with the CDC and others, in terms of taking a 40-page document and condensing it to two pages, and creating a multi-person, creative ways by which we can get group consent and move through the process, there's still a lot of enormous work involved there. We need to deal with things like language barriers. We need to deal with health literacy. I mean, these

are things I see where I work in terms of trying to consent people for just standard things.

And then, of course, there's the crisis of death and the fear of death, and how you obtain informed consent with the threat of death over the whole process is another ethical question. I mean, the last issue is whether it's safe, whether the vaccine itself or any countermeasure would pose risks to the population that's going to be studied in that, but, again, I think the framework has to shift here because we're going to be paralyzed by risk. And I am, again, suggesting that maybe we should also spend some time thinking through that for any such design, any protocol. This could be about anything. It's not just about anthrax.

CHAIRMAN BOTKIN: Dr. Wilfond?

DR. WILFOND: Again, I'm going to talk to you with my back to you. I had something that maybe does relate slightly to the question about benefit, possibly because your very last comment, or second to last comment, that talked about age de-escalation, I was thinking about that, and I'm not sure I fully understand why you think age de-escalation makes sense versus just doing it in a wide range of ages. And the reason why I was saying that is that, presumably, vaccinations, it may just be if it's different in different ages, it may actually be even safer, for example, on younger kids than older kids. I don't know

that. But it just struck me as being a very interesting question. So I'm just curious as to why you thought we should do that de-escalation, and what ranges you were imagining we should do that with?

DR. FAGBUYI: So, thank you, great point. I think the issue was what recommendations were out there, and what the USG was saying there was an open window of opportunity. Age de-escalation was an issue that was brought up, but I think it's an avenue to move forward. There are developmental gaps and issues that need to be addressed. So I use the example of a 15-, 16-, 17-year-old kid. Probably, it's reasonable to say that they're probably about the same, and they may react almost the same. Some could argue maybe 12-, or 13-, 14-year-old may react the same. But there may be some developmental issues that need to be considered.

I'm not the one doing the research protocol, and I'm not advocating for any research protocol specifically. But I think if we do broad ranges, you may not be able to pick up on little signals that you may need to pick up on in these types of settings. So that's why I was saying that.

If you just use broad ranges, there are some kids that'll react more, and the people who do this very well may be able to comment better on this. But certain kids, I know, when I was actually practicing pediatrics as a practitioner where I

had patients, I gave shots to there's some where you can give them a shot in the arm, and they have this massive swelling, and they cry, and there's an emotional component. So that may be defined as risk and harm that the parents just can't stomach, whereas the older kids didn't have that reaction. But then again, you could also argue the flipside, where there's a 16-year-old teen that comes in for a sore throat, I do a rapid strep, and she's screaming bloody murder, as if there were something else going on, whereas it's just as well.

But I think the age de-escalation opens the opportunity to be able to begin this, or else we'll continue to be paralyzed by the issue, "Was this risk? And it's a little kid. We're not going to move forward," and we won't get the job done.

CHAIRMAN BOTKIN: Dr. Kopelman?

DR. KOPELMAN: Yes, thank you for your very clear and thoughtful presentation. I'm somewhat worried about adopting a very broad definition for "condition" for the usual use of the regulations. For example, poverty and obesity are associated. But unless you do the hard work of finding the intervening variables, do you really justify going up on research risk? And I would say just an association isn't really enough. Others will benefit from the studies other than the poor, and I think

it could be very socially destabilizing if before now, there's one set of risk for them and another for others.

Also, a condition could just drop out as being a necessary condition, if everything's a condition. So my question to you is, do you mean a broad definition of condition for the purposes of countermeasures, or do you mean it in general?

DR. FAGBUYI: Thank you very much for that clarifying question. Yes, specifically medical countermeasures. I think medical countermeasures is just in a different realm, honestly. I don't think when we think of regular research, for example bench or clinical research, where we are intervening with patients with routine, or regular, or normative research, that's fine. But when we're talking about medical countermeasures, which are medications, antitoxins, equipment, and things that are supposed to be lifesaving to a public for a significant risk, that, I think, is totally different. And that's the scenario for which I'm saying you would use "condition" because you would say they're at risk for this disease. Tularemia, they're all going to get pneumonia, and there's a 50 percent chance of everybody dying. The LD50 is X, Y, and Z, and we're going to treat this whole certain population of this geographic area because of X, Y, and Z. That's the population I'm talking about. Thank you.

CHAIRMAN BOTKIN: Dr. Bradley.

DR. BRADLEY: Thanks very much, Dan, for putting a nice clinical spin on the issues.

During the anthrax and the botulism working groups, actually, some of the risks and ethics had come up, not nearly in the detail that's being brought up in this particular group, but things are being considered. In an event where you want to get all of your mitigation treatments and vaccines to as many kids as quickly as possible to prevent death and suffering, we're trying to work to get the drugs and vaccines to them as safely as possible, we've mentioned the EUA and the IND ways to do this. One, the EUA doesn't require the informed consent but discussion, as Steve had mentioned, and it only requires an informed consent. And actually, in the anthrax working group, to have both of those in place at the same time was discussed, because I actually want to know what the protective effect of the vaccine is, even though I want to get the vaccine to everyone. So I would fully support an IND and EUA at the same time; they're not exclusionary. And you can get people to commit for a vaccine study, a full vaccine study, with blood draws at, you know, five days, seven days, 14 days, a month, two months, the way we normally do.

The other issue with risk mitigation, we're recommending antibiotics, as Steve had mentioned, for 60 days.

The ones that are recommended are ciprofloxacin and doxycycline. There are no safety data for 60 days' worth of treatments. Not only will the kids not take them, the way Steve's mentioned, but what are the toxicities? Are there cartilage toxicities of sixty days of fluoroquinolones in children? This worries me. Are their brittle bones going to be a consequence of doxycycline for 60 days?

And we talked about this in the working group. Some of this is incorporated to the guidance that we're creating in the CDC. But I would love to see research that would allow us to put a number on risk-adverse events for these medical countermeasures that we're actually recommending for which we have no data, that the FDA is working with us so that if, heaven forbid, there is an event, we will know much more about the safety of these drugs and vaccines.

CHAIRMAN BOTKIN: Thank you. Dr. Fagbuyi, thank you very much.

OPEN PUBLIC COMMENTS

CHAIRMAN BOTKIN: All right, we're going to turn now, since it's 2:00, to the public comments, and apologize to Dr. DeGrazia. Hopefully we'll be able to drop back into our schedule after the public comments. So I have a statement here that I'll read.

This is the point in our meeting when we're open for public comments, and there's a statement I read to be in this process. "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Pediatric Ethics Subcommittee Meeting, the FDA believes it's important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement, to advise the Committee of any financial relationships that you may have with any firm or any group, their products, and, if known, their direct competitors. It's likely to be impacted by the topic you address in your presentation. For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial

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

Walt, do you want to make the first?

DR. ELLENBERG: All right, thank you. As we begin the open public session, I just want to let you know that in preparation for this meeting, we received one written comment from Dr. Cara O'Neill, assistant professor of Pediatrics at the University of South Carolina School of Medicine. Dr. O'Neill's statement is in the three-ring binder outside and is available for you all to read as you leave. And that was the only written comment that we received. Her statement will be added to the record for your review.

As far as open public session speakers, we received a request from one individual, or actually one organization. And Dr. Michael Carome, who is the Director of Health Research Group for Public Citizen here in Washington, D.C., who will present a short slide presentation. It should be 10 minutes. We will start it as soon as I get up to the podium. Dr. Carome, would you check your microphone just to make sure it's on?

DR. CAROME: Testing. Well, good afternoon. My name is Dr. Mike Carome. I'm the Director of Public Citizen Health Research Group. Next slide, please.

So I'm briefly going to make some comments about the definition of minimal risks. I'm then going to address some of the questions that were raised in the background material regarding 21 CFR 50.54. And then, although you were precluded it seems, I'd like to talk about a specific vaccine trial. I'm going to make some comments about the preventative raxibacumab vaccine for children that have been proposed, and I think forms the framework for some of the discussion that's occurred meeting. Next slide, please.

So you're all familiar with the definition of minimal risk. I won't go over it again. Next slide.

So our organization endorses an interpretation of the regulatory definition of minimal risk that uses the uniform standard framework. And my sense is that many here agree with that, so I'm going to go through this quickly. Next slide.

So, many groups have opined upon how to interpret the definition of using the uniform standard. One is the IOM Committee on Clinical Research Involving Children. And they stated that on ethical grounds, the committee rejected a relative interpretation of the definition of minimal risk. That is an interpretation that allows the application of higher thresholds of risk for children who experience higher risks in daily lives as a result of their place of residence, family situation, medical condition. Instead, the assessment of risk

should be indexed to the experience of the average, normal, healthy children. Next slide.

So on the basis of that thought process, they have recommended in Recommendation 401 that in evaluating potential harm to discomforts posed by research protocols that include children, interpret minimal risk in relationship to the normal experiences of average, healthy, normal children, and focus on the equivalents of potential harms or discomforts, anticipate in research with the harms or discomforts that average, healthy children experience in daily life or during routine physical or psychological examinations. Next slide.

They noted also in the committee that the relative interpretation of the minimal risk standard is inconsistent, both with an ordinary or commonsense understanding of the concept of minimal risk, and with the objectives of providing special protections to children participants research. Next slide.

And this framework, this thought process that the IOM committee made, this is reflected in multiple other federal bodies that have opined on the topic, and I've listed some here. Next slide.

Turning now, I'd like to make a few comments about the standards that 21 CFR 50.54 applies to research, and raise a question about whether those standards potentially could offer a

lower standard of research that might be allotted under standard category 50.53. And so I've listed here the three major findings that a committee would have to make convened by the Secretary of the Commission of FDA and approving research under 50.54. And they include that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; will be conducted in accordance with sound, ethical principles; and that there are adequate provisions for soliciting parental permission.

And I note that the second and third provisions there would apply to all research. So those aren't unique to this category. So we're left with just that first bullet as perhaps providing the unique standard that is supposed to be applied to this research. Next slide.

And let's compare that to what the standard would be under 21 CFR 50.53, which says, "The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder condition that is of vital importance for the understanding or amelioration of the subject's disorder condition." And one could recently argued that the standard under 50.53 is more stringent than that that appears to be under 50.54. So, next slide.

So the IOM Committee on Research involving Children talked about this issue, and they noted the following: As described in the 1977 report of the National Commission, the referral proposed a research for national review should be reserved for exceptional situations and research of major significance. Given this context, the committee believes that the criterion for judging the potential contribution of research must ethically be as stringent for reviews conducted under Section 407, or 50.54, as those conducted under Section 406, or 50.53. Thus, although it's not required by the regulations, the standard of vital importance should be applied by the panels involved in the review of proposals by the secretary or the commissioner for 50.54 research. Next slide, please.

Let me just make a few comments regarding some of the issues being raised in the context of 50.54. We would note that we believe the degree of uncertainty about the need for future use of a product should be taken into consideration when evaluating research involving children under 21 CFR 50.54. We believe that's also important to consider the availability of existing FDA-approved products that could be used as countermeasures to expose your children, and that is an equally important consideration. Next slide.

In terms of the issue of transparency, some of the discussion began on this issue this morning. We believe that

all relevant information, including sensitive information that may be classified, should be made publicly available for research studies that are to be reviewed under 21 CFR 50.54. Such transparency is essential to allow meaningful informed input from the public. It's also, I think, essential to buying in public trust at a time when, many times, there's a lack of trust in activities convened by our government. Next slide.

Let me now make some comments about the proposed vaccine study on anthrax that's previously been discussed by other bodies. And the views I'm voicing today, I believe, expressed previously in writing and publicly, in letters the Secretary of Health and Human Services and to the President's Commission on Bioethics.

So we strongly oppose the conduct of pre-event clinical trials of the anthrax vaccine in children. We believe that such trials would be unethical and are not approvable under the HHS and FDA regulations for protection of human subjects. We believe that such research does not present any prospect of direct benefit to the children who will be the subject of that research. And we believe that the vaccine does pose significant known risks of potentially serious harms, and the research testing vaccine would involve greater than minimal risks and greater than a minor increase over minimal risks. Next slide.

The package insert for the product that would be tested lists many serious risks, which are known. It's likely that the probability of some of these risks is lower than is known because many adverse events for products don't get reported. Next slide.

So, some of these risks include anaphylaxis, serious allergic reactions. And some of these reactions may be multi-systemic and chronic. Next slide.

We believe that such research could only be conducted if the requirements of the FDA regulations of 21 CFR 50.54 were satisfied, and that they would include the research presents a reasonable opportunity to further the understanding, prevention, alleviation of serious medical problems, and conducted in accordance with the sound ethical principles and addressing those two issues. Next slide.

We believe that regarding the first determination, anthrax, currently, we believe, is not a serious health problem affecting the health and welfare of children in the U.S. In the extremely remote chance that children would be exposed to anthrax, it is not sufficient justification for testing the vaccine in children, particularly since there are antibiotics approved by the FDA for use in children to treat post-exposure cutaneous or inhalation anthrax, including the two listed there.

It's also been noted to date that some of the countermeasures that might be tested, like the anthrax vaccine, there are pathways to using those if people believe they offer some benefit to children in the event of a post-exposure event. Next slide.

Regarding the second determination, the proposed research would not be consistent with sound ethical principles because exposing vulnerable children who lack autonomy to make an independent decision about participation in research to a higher-risk experiment intervention is not justified, given the lack of any direct method to those subjects and the fact that anthrax is not a serious health problem affecting the health and welfare of children. Next slide.

We note that millions of taxpayer dollars are being spent currently to maintain a national stockpile anthrax vaccine and other common measures. And exaggerating the risk of the anthrax or other bioterrorist event for both adults and children may help justify such expenditures, which would not be used to justify ethical research in children. Next slide.

So, in conclusion, given the known risks of the anthrax vaccine, we disagree with the proposal by the Presidential Commission for the Study of Bioethical Issues that careful age de-escalation experiments in adults and independent older children might be an allowable pathway to infer that

studies involving children will involve no more than minimal risk. We believe the risks are known, and that is not an appropriate strategy. Next slide, which is my last slide.

So, pre-event clinical trials in children testing greater than minimal risk experimental medical countermeasures against unlikely exposure to various biologic or chemical agents, such as the proposed anthrax vaccine, should not be permitted by the FDA or HHS. Thank you for your attention.

CHAIRMAN BOTKIN: Thank you very much. Dr. Wilfond?

DR. WILFOND: Thank you for your presentation. I just want to make sure I understood what you said toward the beginning, and I'm not going to discuss the end since we're not supposed to talk about the vaccine. But the title slides that talked was about 50.54 being a lower threshold, it sounds like what you were saying is that only things that could be approved by 53 should be approved in 54, which would be anything additional that could be approved 54. I'm not sure I understood that.

DR. CAROME: No, I'm just saying that, you know, IOM Committee raises as a concern that when you look at the standards under 50.53, where you have this vital importance standard for serious health problems affecting the health of children, then you turn to a language, the third provision of 50.54, that seems to be a step down from that in terms of its

stringency. So I'm just saying, as the IOM opined, that same strictness of the vital importance of the research, the question to be answered should extend to 50.54. So I wasn't suggesting otherwise.

DR. WILFOND: What should be different, then, between 53 and 54? I'm just trying to make sure I understand what the scope would be.

DR. CAROME: So the difference is that presents a reasonable opportunity to further the understanding, prevention, or alleviation of serious problem affect health or welfare; that's in 50.54. That appears to be less stringent than the language found in 50.53.

DR. WILFOND: Let me try to clarify my question. My question is not how the language is different, but, presumably, the purpose of 50.54 was to carve out a group of studies that could not be approved by 53, and therefore, with public process, potentially could be approved. I was trying to get to the clarification: is what you're saying really is that there shouldn't be any studies, at least that can be approved under 53 should also not be approved under 54? Or if it was, what would those studies be like?

DR. CAROME: No, I think there are other provisions that we haven't talked about. So under 50.53, you have the minor increase over minimal risk. So I'm talking about research

where there is no prospect of direct benefit. There is risk that exceeds the minor increase over minimal risk. And there is no sort of condition in play. So I think there are two things in the affects. I've seen study that don't come to play under 50.53. And so if you're going to review a trial about the vaccine under 50.54, I think you should adhere to the vital important standard in that other provision. Thank you.

REFLECTIONS ON ETHICALLY ACCEPTABLE

RISK IN PEDIATRIC RESEARCH

CHAIRMAN BOTKIN: Okay, thank you again. All right. We're going to proceed on then to our next presenter, Dr. David DeGrazia, who's going to speak about Reflections on Ethically Acceptable Risk in Pediatric Research. Dr. DeGrazia has been working at George Washington University since earning his doctorate, and recently joining Bioethics Department of the NIH. Primary areas of specialization are ethical theory and biomedical ethics. Dr. DeGrazia's publications include over 40 solo-authored journal articles and 30 book chapters and six books. Welcome.

DR. DEGRAZIA: Thank you very much. How is my voice projecting? Are you okay in the back? I have a bit of a cold. Is it good? Okay, good. Glad to hear that.

All right. The views I'm going to present here are my own and don't necessarily reflect the position of NIH or the Presidential Commission, or any other part of the federal government. I mentioned the Presidential Commission because for about half of 2012, I worked part time as an advisor to the staff of the commission.

All right. Let me go over the main ideas of my talk. First, I'm going to suggest that our current ethical regulatory approach to pediatric research is implicitly a rights approach.

Second, the children's right to adequate protection raises the question of what level of risk is consistent with adequate protection. Third, there has always been a question of why we should allow any known risk to pediatric subjects without the prospect of direct benefit, as one or two speakers have already noted today.

I suggest the answer to these is to what might be called the Responsible Parent standard. And this standard suggests a very rough risk ceiling for studies approvable under 45CFR46 Section 407. And I'll be using the HHS reg numbers rather than FDA because I'm only familiar with the former number system.

And finally, having argued this, I will also argue that certain practical considerations recommend against allowing this level of risk in most circumstances. Current regulations, Sections 404 and 406, I think are already quite reasonable in their permitted risk levels. And just to remind you, this, I think Skip designated this as the stretch ethics section. So it may seem a little loud there at times.

Okay, children's rights in this context. I am convinced that the current ethical-regulatory regime is implicitly a rights framework, and, more specifically, a moral rights framework. And I think this is apparent in the way that it sets some strict limits on the involvement of children in

research, and the way in which those limits protect children's vital interests.

I'm going to assume, for convenience in this talk, that children are incapable of informed consent in that robust sense that's legally important. In other words, that they are not adults, although they are often capable of meaningful assent. So in other words, I won't be talking about so-called mature minors who may be capable of voluntary informed consent. So in other words, I'm talking about children who need extra protection.

In particular, as far as rights go, we have the assent requirement, that adequate provisions are made for seeking the assent of child participants. And this, I think, suggests a child's right to meaningful, age-appropriate participation wherever possible in decisions about their involvement in research. This is not to say they're incapable of informed consent and that they're autonomous adults. But autonomy, after all, comes in degrees, and that to the extent that children are capable of participating in these decisions meaningfully, they have a right to do so.

Children's rights are also implicit in permitted risk levels; in particular, a child's right to adequate protection. And I'm going to focus on the second, this right to adequate protection.

Okay, the first, a bit on rights in contrast to goals. I think this is important conceptually and morally. The right to adequate protection is roughly the right not to be subjected to excessive or undue risk. And this serves as a constraint or limit on the pursuit of goals. So I have all sorts of goals, including the goals related to research. In general the goal of biomedical progress is extremely important. What rights do, if they're understood properly, is they set limits on the pursuit of goals. They say, "Go find your destination but don't go through here. This is a limit." And that's why we shouldn't even consider a study that would test the safety of new car seats by involving children in car crashes. Even if you could convince me, convince everyone here, that the information you could gain would be far more helpful and give far more utility than any other study you could do without involving children, we should say, "No, we're not going to do that because doing so would grossly violate the children's right to adequate protection."

So if we understand the function of rights, I think, and appreciate them in this context, we can see that it's misleading and potentially a bit dangerous to talk of balancing subjects' rights with the need for research, or societal good, or utility. And sometimes in the literature you do see this talk of balancing between the two. But if rights are balanced

against the goals of research or the common good, then rights aren't playing their protective function. And they're not really rights. Basically, they're just interests that are kind of along with the interest of the public. And I think that is potentially a serious mistake.

So, some implications of this. One, children have no obligation to participate in non-therapeutic research. Parents, for their part, have no obligation to volunteer their children or encourage them to enroll. Society can hope that children enroll in promising studies, but cannot ethically demand it. And ethically-appropriate studies will respect a child's right to adequate protection.

Okay, sounds good. But what does it mean? What does a child's right to adequate protection come to? I think it's more difficult.

We can interpret the current ethical regulatory regime in this way. Adequate protection actually sets slightly different levels, depending on the context or the circumstances. Adequate protection means no more than minimal risk, in most cases where there's no prospect of direct benefit, as suggested by Section 404. Where there is the prospect of compensating direct benefit, Section 405, then at least no more risk than necessary for that prospect of compensating benefit. And then, of course, no more than a minor increase over minimal risk where

there's no prospect for direct benefit. But the study has promise for illuminating or ameliorating a condition that the pediatric subject has.

Okay, for the moment, I'm going to set aside the very complicated case, or set of cases, the exceptional cases that are relevant for Section 407 before we get there. But wait, here's a question, sort of out-of-the-box question, but I guess it's not too much out of the present box, because at least one other speaker's already mentioned it. I think that was David Wendler, but why tolerate any risk in non-therapeutic pediatric research? I mean, why not just insist on no risk at all? We have come to think of minimal risk as roughly risks comparable to those of everyday life or routine medical exams. You might say, "Well, that's just, you know, that's just ordinary stuff, if we interpret it reasonably. "It's just more of the same sorts of risks that children face generally." But the point is it's more of the same. So if children face some risk in everyday life, no matter what you do, in research that involves some risk to them, you're adding to the risk they already face. And it's not unreasonable to ask whether this is justified.

How can it be acceptable to impose any anticipated net disadvantage on subjects who can't consent? Again, we're assuming they cannot consent in the relevant sense like

competent adults can. And why isn't this just using them as mere means?

My suggestion is that we can understand the answer by thinking a little bit about what we already believe about responsible parenting, and the range of decisions that it can encompass. And that the same idea can help to set a risk ceiling for 407 studies. Now this was all very tentative, I haven't tested out these ideas very much, and so I sort of agree that this is a stretch ethics session, but anyway, I think there's some promise to the idea. That's all I have.

All right, so the Responsible Parent standard. Responsible parenting includes adequate protection of one's children from harm. That's part of what being a good parent means. But here's a key point. Responsible parenting doesn't mean perfect minimization of risk. If you think about this, especially those of you who are parents, it's not really true that you absolutely minimize the risks, you let them do some things that involve risks, and this can be perfectly fine in parental decision making.

So, first, some examples that involve children helping others, as discussed by some other speakers. If you let your child help to clear an elderly neighbor's lawn, and the lawn has some poison ivy, you urge your child to be very careful. But unless the child has an extreme allergy to poison ivy, you would

not seem over the top or irresponsible to allow them to take this non-zero risk in helping the elderly neighbor. Or you might allow a child to bring groceries by bicycle to a needy person's home. You could imagine the child putting the groceries in a backpack, you know, there's a slight chance of something bad happening, you want to make sure your child is good at riding a bike and so on, but if he or she is not too young, this might be a responsible decision. Or imagine another child running in an eight-kilometer race on a day that happens to be rainy, and the basic purpose for running in the race is to raise funds for charity. In none of these three examples do I have the reaction that the decision to allow the child to participate would clearly be irresponsible. Depending on details, it seems it could be perfectly responsible, even though you're not minimizing the risk for your kid.

Now there's another kind of example that involves the interests of parents, or there could be other members of the family. Imagine a stay-at-home mother, or could be father, who decides that, after years of being at home, returning to the workforce and resuming a career is really important to his or her flourishing. And let's imagine that by their best estimates, it would be a little bit disadvantage to one of the kids; not devastating, the kid's still well cared for, but a little bit disadvantageous. I don't think we can judge in the

circumstance it would be wrong of the stay-at-home mother or father to return to the workforce even if there's a slight disadvantage to one of their kids.

Another kind of more everyday example, a couple wants to go out to dinner, they almost feel like they need to go out to dinner to get away from the house maybe. The kid doesn't want to go, but isn't old enough to stay at home, not really time to get a babysitter, they make their kid go to dinner with them. This is not the best thing for this kid right now, you could supply details to make sure that that's plausible, but it might be a perfectly fine parenting decision, because although children's interests are paramount, and they have rights to adequate protection, food and shelter, and so on, that doesn't mean you literally have to maximize their best interests all the time.

How is this relevant to research? Well, pediatric research ethics does not require always promoting what is literally in a child's best interests. The phrase "best interests" sounds good, it sounds morally serious and the sort of thing that you'd want to live up to, but I think we have to admit that if you take it literally, it's a little bit exaggerated. Rather, what sets appropriate standards, and I think what sort of designates the contour of their moral right,

is a child's essential or vital interests, including adequate, if not perfect, protection.

So let me elaborate. What constitutes adequate protection? Well, I would say at least as much protection as responsible parents would provide their children. Now, I am fully aware that this is very imprecise. I hope it can be helpful even if it's imprecise. And I also am well aware that there's no one template for what risks responsible parents would allow their children. Different parents have different styles and different levels of risk aversion, and that's all just fine. We do, I think, appreciate there are some risks that it would be irresponsible to impose on children. For example, if you let your 8-year-old go collect donations door-to-door by themselves in a very dangerous neighborhood where there's a lot of gang violence, I mean, this would be over the top; it's just way too risky and not responsible. So my suggestion is that while there are a lot of different parenting styles and there's no one template, there are some judgments about risks that clearly are okay and some judgments about risks that are clearly not okay, even if there's a fair amount of gray sometimes in between.

So the standard I'm suggesting is something like this: The highest level of permissible risk in any pediatric study is the most that some responsible parents would permit for their children in activities whose basic purpose is to benefit others.

Or, to put it another way, since even responsible parents can sometimes make mistakes, I'll put it in terms of responsible parenting, the highest level of permissible risk in any pediatric study is the most that is consistent with responsible parenting regarding children's activities whose basic purpose is to benefit others.

I think of this level of risk, and I don't know what term to use exactly. I am thinking of the term relatively minor risk. It's still relatively minor, but I think it's maybe a little bit more inclusive than a minor increment over minimal risk. And it may be a promising ceiling for studies that might be approvable under Section 407, assuming other relevant conditions are met. Speaking of which, if something like this is appropriate for the maximum allowable risk in non-therapeutic pediatric studies, it's important to remember that it's only one ethically necessary condition. There are others, for example, not forcing a dissenting child to participate, and taking seriously the best available alternative that either imposes less risk or offers the prospect of direct benefits. In other words, I would never justify a view according to which as long as the risk is relatively minor, then it's okay because the risk may be more than it needs to be, or the study might not be very important, or there might be other ways of getting the information.

And the standard is imprecise, again, and doesn't eliminate the need for thoughtful deliberation in particular cases. My guess is the best we can do is suggest a standard that's a kind of heuristic that helps us focus our attention, but I doubt we'll ever be able to suggest one that's terribly precise and eliminates the need for thoughtful people talking back and forth and really thinking hard about whether the standard applies in some cases that are not obvious.

What I've said raises a question: If all this is on the right track, should this standard replace other standards in pediatric research? If I could have my way, would I just do away with 403 or 406 and the standards they incorporate? Probably not. I've suggested this responsible parent standard allowing relatively minor risk as a ceiling for 407 studies, along with other important ethical conditions, but I'm not suggesting that you replace minimal risk for a minor increment over minimal risk across the board. In a perfect world, maybe so. Maybe in a perfect world where no one had any biases, and everyone was really impartial, and trust was universal and well deserved, and your great calculators of consequences, maybe, maybe we could just allow this relatively minor risk across the board. But in our imperfect world, I would not recommend that.

And somebody mentioned some reasons to retain the current standards in nearly all cases. First, there's the

phenomenon of asymmetries of power, where government is involved in some way in conducting research, government generally has more power than individual decision makers, and investigators and physicians often have more than children and their parents. There's also an important difference in relationships to particular children. Parents, normally and appropriately, have great affection and protective instincts towards their children, and this is really important even when they're making decisions, or maybe especially where they're making decisions that permit some risk for their children. Government officials and investigators can't be expected to have the same spontaneous affection and protective instincts toward particular children who are not their own children, and this is, I think, an important difference to notice.

Also, conflicts of interest and related biases. Now, please understand in using the term "conflicts of interest," I'm not assuming an accusatory tone at all. I just mean to acknowledge certain interests in particular agencies or enterprises that can be reasonably expected to result fairly often in biases in the part of individuals who occupy the relevant roles. Investigators' interest in career advancement, I would think would tend to generate a pro-research bias. More broadly, biomedicine's interest in biomedical progress makes them very interested in research and pro-research bias. DoD and

Homeland Security's interest in public security and safety presumably can be expected to generate a kind of pro-research bias, for example, with MCM studies. FDA's interest in safe products should be expected to generate somewhat of a pro-testing bias, and drug companies' interest in profits should also be expected to generate something of a pro-testing bias.

Now, again, not striking an accusatory tone, but just trying to be realistic. So in our imperfect world, with human beings as we know them, we should go, I think, to great lengths to protect children who may enroll in studies. So while the relatively minor risk standard may be appropriate in principle for non-therapeutic pediatric research as a ceiling, these real-world considerations I've just been talking about exert downward pressure on appropriate risk levels in most cases. But I also suggest that this downward pressure can be relaxed in extraordinary circumstances where 407 approval would be appropriate. Now, in these cases, where the extra protective pressure is relaxed, allowing the risk ceiling to rise somewhat, although the substantive protection is relaxed, the procedural protection increases because we proceed to national review with greater, more of a procedural safeguard.

All right, so some practical implications. When would a higher level of risk that is higher than a minor increment over minimal be justified? Well, not when the research can be

realistically pursued with a lower level of risk. It may seem obvious, but in practice, this may be important. Not when the anticipated benefit isn't much greater than that of the best alternative that features less risk or the prospect of direct benefit, and only when the research is extremely important. There are other conditions as well.

So let's consider some scenarios. I'm a little reluctant to do this, but Skip seemed to want me to, so we'll give it a go. And keep in mind that my judgments really are tentative and dependent on the expert judgment of scientists about the risks and other factual matters. All right. So consider a pre-event study of Anthrax Vaccine Absorbed with children in ordinary circumstances. Here, it seems to me, there's little or no basis for predicting an event involving the release of anthrax. If there were one, then I take it children would be given AVA, a vaccine already partially tested on adults, and antibiotics, as we've discussed, and a post-event trial would begin. This alternative, I think, should not be forgotten. And, of course, in this scenario, where there's already been an event, the study could easily be approved under 405, direct benefit to the pediatric subjects.

With no event being imminent, though, there is time for age de-escalation trials, which might be a good idea, and the thinking goes, this could keep risks to subjects minimal by

starting with trials on the oldest minors whose bodies are quite similar to the youngest adults on whom they've been tested and gradually moving down so that there aren't quantum leaps. So in view of these and other considerations, I don't see a compelling argument for a higher level of risk for this research study.

Contrast, though, a pre-event trial where there's a concrete reason to expect an event. And here's a scenario that was imagined by the Presidential Commission in the report on Page 65. I know we're not supposed to talk about the report, and I'm not really doing that, I'm just using one of their examples, and I didn't want to plagiarize, that's all.

So imagine that large amounts of weaponized sarin gas, which I am told is estimated to be about 500 times as toxic as cyanide, have disappeared under suspicious circumstances. A new medical countermeasure is promising, but hasn't been tested on children. That's the scenario. Now in a case like this, there may not be time for age de-escalating trials. The threat seems great, and it's not merely theoretical anymore; there's reason to think it really might be around the corner. So depending on further details, I would say this looks like a promising example of a trial that would justify higher risk. Still relatively minor risk, as I suggested for 407, unless the probability of an attack seems so high that we're basically expecting one. Not just thinking there's a scary chance that it could happen, but

we think it's extremely likely to happen. Then at that point, you could probably shift to 405 and talk about direct medical benefit, and then you could, if necessary, and hopefully you wouldn't have to, but you could theoretically tolerate even higher risk.

And here's a protocol, I guess it was considered by your subcommittee, the trial of something hard to pronounce, which I'll call GCSF, stimulated bone marrow versus conventional bone marrow as a stem cell source in matched sibling donor transplantation. I gather that the hope was to find a better way to treat children who have leukemia using bone marrow from an HLA-identical sibling. There's no direct benefit and prospect for the donor sibling. Of course there is for the recipient sibling, but focusing on the donor sibling, whose interests have to be taken into account, no direct benefit and prospect, so this wouldn't fit Section 405. Also, at least on my understanding, the donor sibling does not have a condition in any relevant sense relevant to 406, and the subcommittee found the risk to be higher than a minor increase over minimal risk. But the risk, as far as I can see, looks like it's still relatively minor and would be consistent, I think, with responsible parenting to permit this level of risk.

I have to admit, another consideration comes in for me. It's not supposed to come in according to the, you know

sort of current regulatory ethical regime, the prospect of indirect benefit. It seems to me that if the relationship between the siblings is at all healthy, there's a prospect of a massive indirect benefit, namely that a greater chance of your beloved sibling surviving, and I think I can't just ignore that, and because of that, it may make this case easier for me. But I think even without that, this sort of case might be approvable under the rough standard that I'm suggesting here.

And thank you for your attention. Before I finish, let me acknowledge that my thinking has benefited from discussions with a number of people including especially Michelle Roman, Lisa Lee, and Dave Wendler.

CHAIRMAN BOTKIN: Thank you very much.

DR. DEGRAZIA: Oh, stay here?

CHAIRMAN BOTKIN: Yeah, stay there, and I'm going to they're probably going to ask a question. Going back to the responsible parent standard that you articulated, it wasn't clear to me how those standards were going to be derived. Are they derived conceptually from what we think responsible parents should agree to, or would this be influenced by a data collection process where we would see what responsible parents actually do agree to? Or would it be both?

DR. DEGRAZIA: Or maybe neither. I think it would be based on our beliefs about what levels of risk in particular

contexts are consistent with responsible parenting, and what level of risks are not, considering a wide variety of cases. But one could do empirical studies to make this more scientifically rigorous. It wasn't the way I imagined it, because I thought in a lot of cases our intuitions are fairly clear that it's consistent with responsible parenting to allow your kid to do this or that. You'd have to fill in details about their age, maturity, and physical health. But the idea is that we already have available, in a sense, our own commonsense judgments about good and bad parenting, responsible and irresponsible parenting, in that we notice that responsible parenting does allow toleration of some risks for children, even when it's not for their own benefit, but for the benefit of some others.

So this plugs in somewhat with the discussion about altruism and charity that went on earlier, in that if we're reasonably confident in these judgments, we may think that they suggest a standard for a ceiling of allowable risk and research. And then I suggest we also consider those various practical considerations that suggest even more protection in most cases. Basically, the relationship between a parent and a child is different from the relationship between a research institution or the government and a particular child.

CHAIRMAN BOTKIN: Loretta?

DR. KOPELMAN: Hi, thank you, David, I enjoyed it. I have a question also about the scrupulous parents. You admit that you disagree that some think the 407 study is okay and others might not. At what point do you know some parents are not being scrupulous? A lot of them disagree, "Oh, I wouldn't put my child in that setting," and if you do, how do you decide who's not a responsible parent for this child, and I know there are other necessary conditions, but, I mean, for the point of your concept, child abuse would be a way low standard, which is kind of illegal, then. So who's not scrupulous?

DR. DEGRAZIA: Well, the one example I gave is the parents who would allow their, what was it, 8-year-old to go door to door in a crime-ridden neighborhood collecting donations for a charity. And I'm imagining a neighborhood that's really quite nasty, where there's actually gang warfare, and so on.

DR. KOPELMAN: I was thinking of a research setting, where you might have a nasty neighborhood too, but I hope not, where you might have investigators enthusiastic to find some parents willing to go along.

DR. DEGRAZIA: Well, to some extent, the standard would rely on the integrity of decision makers not to sort of make the invalid inference that if some parent would allow this, therefore, it's responsible, because that, of course, would be hellacious. But what I would suggest is only allowing more than

a minor increment over minimal risk in some 407 context. There would be plenty of opportunity to get people together to talk about whether it really would be responsible for any parent to allow this level of risk for their children, and so it's not the sort of approach that would be plagued by isolated investigators making sort of quirky or irresponsible judgments. The procedural protections are fairly significant.

But one thing I want to definitely grant you is I've not yet thought carefully about how close I can come to drawing a line about what the ceiling would look like. I've just noticed that there seem to be cases that are clearly irresponsible and there are cases that are clearly responsible.

DR. KOPELMAN: Well, the point I'm making is isn't it those other considerations that are really important? So I'll just stop there.

DR. DEGRAZIA: Well, they are important, yes. But this would allow consideration of a bit higher risk level than, say, 406 allows, for whatever that's worth. And I assume that in some cases that actually is an important difference.

CHAIRMAN BOTKIN: All right, I got a long list here, I believe Dr. Krug was next.

DR. KRUG: Thank you. Steve Krug. Thank you for bringing up the issue of reasonable parenting because I agree with you. Let's just briefly move away from the concept of

research. That's the standard that clinicians use in how we evaluate and treat children, particularly children who are not empowered to consent on their own. And sometimes the parents don't really want us to do what we think is in the best interest of the child, and at times, it might even be endangering the life of the child, and much more often than not, substantially more often than not, we can explain to reasonable parents why that benefit is there, why we should stick a needle in that child's back, as an example, and --

DR. DEGRAZIA: For that child.

DR. KRUG: For that child, not the adult's back.

DR. DEGRAZIA: No, I mean benefits for the child.

DR. KRUG: Yeah, and, you know, for a lumbar puncture, and make that happen. So it makes total sense to, again, not to throw out the other ethical review processes, but to use that as a reasonable ceiling. I think it actually does work. You also brought up something else that I thought was quite pertinent. And again, for any biologic vaccine that we might be talking about, you could, I guess, evaluate in two ways. One, you could evaluate it in a pre-event setting through the appropriate process, or you can evaluate it because now it's actually time to vaccinate everybody because the germ is out there, and we have now engaged in a public health process where we are vaccinating everybody, or everybody within a particular area.

You can argue, and it's been suggested, that it's somehow a lower risk scenario. I would actually be interested in your thoughts on this. I think it's actually a higher risk scenario, but the apparent benefit may be greater because the germ is floating around in the air. And because of considering all the potential side effects that one of the public speakers brought up, the ability to monitor the enrollees thoughtfully, meticulously, and provide care for them in a midst of a public health crisis, I suspect, is slightly less.

DR. DEGRAZIA: Yes, I agree that I think the risk would be higher but the prospect of direct benefit would justify a higher level of risk. On the other hand, preparations in advance might make things smoother in some of those risks.

CHAIRMAN BOTKIN: Dr. Fost.

DR. FOST: Norm Fost, David, that was great. But you kept talking about this is extreme ethics or something like that.

DR. DEGRAZIA: A stretch.

DR. FOST: Oh, yeah, stretch ethics, but I'm not sure if you went far enough. So there's two questions I have for you. First, I'm told that the oldest law that anybody knows about is the law of battery, that when ancient societies got together, this was the first thing they agreed on, no hitting, no unconsented touching, and all societies take that seriously,

and you can agree that laws are simply a writing down what people think about the ethical issues. It seems to be very basic, and fourth degree battery is just a mere unconsented touching. And this is Paul Ramsey's position, battery is just wrong.

So none of your examples of a responsible parenting included battery: mowing the lawn, even going into a high-risk neighborhood, which is admittedly more risky than a lot of these assertions. But this principle of battery is very deeply engrained. So I don't know that you do allow parents to stick needles into the kid.

DR. DEGRAZIA: How about getting a haircut they don't want?

DR. FOST: It's not quite invasion the body, I mean, it's a little bit outside of that.

So that gets me to infants, and I'm glad that you used the word "dissent" rather than "assent" because I think the principle behind it is, as you implied, that no means no. That under no circumstances should a child be physically coerced, and be strapped down and held by strong team, and then have a needles jammed into him or her just because there's some benefit to society.

So what about infants or very young children who are dissenting for exactly the same reason that you and I dissent to

joining on therapeutic studies, we just don't want to do it. I mean, it's just annoying, it's aggravating, we have time considerations also. But when an 18-year-old says no to a non-therapeutic needle, I think she's saying, "I just don't want to be stuck by a needle," and that's what the 6-month-olds or 2-year-olds are telling us, they express it as clearly as they know how, but the reason is pretty much the same. It's just aggravating, annoying, uncomfortable, and so on.

So if dissent is to be taken seriously, how can any non-therapeutic needle sticks be justified in infants and small children?

DR. DEGRAZIA: You raise a tricky question about how to understand the assent requirement. Does it go all the way down, or does it only go down to those children who can have some understanding of why you want --

DR. FOST: That's the present understanding, but I'm asking why that limit? If the reason is that battery is wrong, and no means no.

DR. DEGRAZIA: Well, for one thing, unconsented touching is not wrong if/when it's necessary for that individual's well-being, but we're not talking about that kind of case. I'm not sure about involving infants in non-therapeutic research that causes them distress. I'm not sure

about that, actually. I have not decided what I think about that kind of case.

For those who are, though, it may be fair to say that we're interested not in just any assent or dissent, toleration or resisting, but meaningful assent or dissent, which might imply at least a little bit of understanding of what's going on and why. And if that's the case, then the standard doesn't go all the way down to infants.

DR. FOST: Excuse me, Jeff, if I can just make one brief here. You don't require that of the 7- or the 10-year-old. You don't say, "Give me a reason or show me that you understand," and that even if we did, the reason would be, "I just don't want to get stuck by a needle."

DR. DEGRAZIA: Right.

DR. FOST: And that's the exact same reason the 2-year-old doesn't want it.

DR. DEGRAZIA: Yeah. Well, I mean, one risk of doing it over anyone's dissent is causing them psychological harm. So the right I mentioned to age-appropriate meaningful participation in decision making, now that, stated as such, doesn't seem to apply to infants. But where it does apply, there's an autonomy-related reason for this, right? That is, children typically have partial autonomy because autonomy is not all or nothing. But the other factor applies even in infants,

and that other factor is psychological harm. And dissent is signaling that if you continue, you may cause psychological harm, and that would go all the way down to neonates, I think. But I think it's also fair to say I haven't worked all of this out with that requirement and how far it goes down. Thank you for your question.

CHAIRMAN BOTKIN: All right. Here's my list right now. So, Joffe, Daum, Bradley, Nelson, Glantz, and Wilfond. So, David?

DR. DEGRAZIA: I should've used John Rossi's strategy and talked so long that there was no time for questions.

[laughter]

MALE SPEAKER: Twenty-nine minutes.

DR. DEGRAZIA: Okay.

DR. JOFFE: Steve Joffe. Thanks very much for your talk. One quick one, and then one that may be less quick. So on about the third or fourth slide, you came quickly to the conclusion that children have no obligation to participate in non-therapeutic research. And I just want to challenge that or suggest that that's not sort of a universally-held position.

First of all, there have been arguments worked out that I'm quite sympathetic to, that people in general have prima facie obligations, not necessarily enforceable obligations, but prima facie moral obligations to participate in research from a

risks, burdens, et cetera, level. I see no reason, first of all, why we can't extend that to children. And, as we know, Richard McCormack, you know, said in a long essay in response to Paul Ramsey, that when we can do things that are helpful at no cost to ourselves, that are beneficial to other people, other children, then we ought to do so, and we should want to do so because we ought to do so. So, there's an "ought" there, right?

So, that's the short point, but the longer point actually goes back to John Rossi's talk. He sort of brought up the ideal spectator view. So you could envision that we step back and we say, what scheme of limitations on pediatrics research do we have? And so if we go all the way to one side of the scheme, the most permissive side, say, on one hand, there may be benefits from doing that. We may learn things that may be valuable, but that would allow us to do unconscionable things with some, you know, some small number of children in order to learn those things that we when to learn. We go all the way in the other direction, we say to ourselves, "Well, we can't, you know, go all the way," for example, the way Paul Ramey was, "Well, we can't learn anything, and children, as a class, have suffered greatly from adopting this extremely reductive stance." So the question then becomes, where in the middle are we. And I don't know of any sort of determinate way to come to a fixed

answer about the right place in the middle of that spectrum or distribution might be.

I was sitting here listening to your talk, thinking about whether the responsible parent standard, or if it's just another sort of heuristic for trying to answer that question, or would it end us up in a different place than this sort of veil of ignorance or ideal spectator kind of approach?

DR. DEGRAZIA: Yeah, good questions. As far as that spectrum goes, I think that reflections on or judgments about responsible and irresponsible parenting in relation to permitted risks for children suggests that the standard of not allowing any risks for non-therapeutic research, pediatric research, that that's too strict. And so I think there's a pretty good way of arguing that that sort of arch deontologist is mistaken, right? On the other hand, I am prepared and have asserted a child's right to adequate protection, and that suggests keeping the permissible risks pretty small and not starting to think of them as mere means for social utilities. So my position is incompatible with a direct form of utilitarianism, for example. It's compatible with indirect forms of consequentialism, I think, but I don't want to get into that too much.

So that's the beginning of a way of addressing your second question, I think. The first question was -- can you remind me?

DR. JOFFE: It was just to make the point that there are arguments of why children may have obligations, prima facie moral obligations to participate in at least some kinds of non-therapeutic research.

DR. DEGRAZIA: Yes, I guess I should be a little more open to that, because I do think that adults at least have obligations to make the world a better place. I'm not a libertarian. I believe that we all have obligations to help those in need, but I do respect the point that there are many ways of doing this. And it might not turn out that we have very specific obligations to make the world a better place in specific ways, such as enrolling in studies and so on. So even if we have those moderately strong positive obligations, it wouldn't follow that each of us has an obligation to enroll in non-therapeutic studies. But even if it did for adults, I guess you could say if you thought it extended to children, they too have some obligation to enroll in studies, but if they don't want to, you don't press the point, because at that point about dissent, right? But thank you. I think I was a little quick on that.

DR. DAUM: So my question that I'd like to hear your thoughts on exposes me as a relative newbie to this process. And it seem to me, I'm hearing the word "risk" over and over again. And risk can't be evaluated, in my mind, as an absolute.

So if, for example, the risk of, and I hate that word, I don't mean to use it twice. If the probability of an intentional exposure event, say anthrax, is high, then the risk to the child participating in the research can be seen in one context. If the probability of an intentional exposure to anthrax is very, very low, or unknown, or close to zero, then the risk to the child should be evaluated, it seems to me, in another context.

DR. DEGRAZIA: Do you mean the permitted risk in research?

DR. DAUM: Yes.

DR. DEGRAZIA: As opposed to the risk posed by the agent, the threat.

DR. DAUM: Well, to me, the risk to the child participating in the research project is dependent on what's going on in the community. That is to say, if it's likely, perhaps certain, that there will be an anthrax attack, then there will be an eagerness to participate in this research, which will be judged at the highest importance and urgent, even if it's non-therapeutic. If the risk is ethereal or extremely low, or unquantifiable, or close to zero, then we can have this discussion in the abstract, because there's no imminent attack, we don't know need to know tomorrow.

It seems to me that this word "risk" is being used in two different contexts. I'm wondering what your thoughts are,

and whether you agree that the need for a child to participate, or the need to even design or do a study among children, would differ, depending on the risk of possible exposure.

DR. DEGRAZIA: That --

DR. DAUM: I'm sorry, the risk of an intentional exposure event.

DR. DEGRAZIA: I mean, that sounds reasonable. I think it’s compatible with what I’ve said. One thing we have to do in these discussions is carefully distinguish when we’re talking about risk, are we talking about the risk of an event, or risks incurred by pediatric subjects in particular trials?

DR. DAUM: I think that’s my central point.

DR. DEGRAZIA: Right, and so when the risk of an event, when the probability, magnitude, et cetera, is very high, it can change the degree of permissible risk in the studies, because it could justify a 407 kind of approval if it’s high enough, and if there aren’t viable alternatives with lower risk. On the other hand, once it gets super high, even before the event has occurred, then we’re really talking about direct benefit, because we actually expect the thing to happen. And so the trial participants could be lucky to be getting an early intervention that could help them. Does that make sense?

DR. DAUM: Yeah, it makes sense. The direct benefit issue wasn't exactly what I was raising, but it seems to me that we have several scenarios here.

DR. DEGRAZIA: Yes.

DR. DAUM: And I haven't heard it framed by all the speakers today in the several-scenario format.

DR. BRADLEY: Thank you. One of my comments was what Bob had mentioned, that the scenario drives our willingness to do a study, and if there's a high probability of an event, which again, we don't know, but since we're talking about medical countermeasures, somebody has some information. I think that should help us balance the risks that we're willing to take with kids.

And your one bullet that it is misleading and dangerous to talk of balancing subjects, right, with the need for research, which later on in your talk, you seemed to soften on that, but that's where Bob's point about the probability of an event which threatens a child can justify some balance the child runs. And we can take the child's rights to be protected from research in the context that we can perhaps prevent death.

Dr. Rossi's lecture, I was hoping to bring the parents into that. So, I appreciate your bringing their role into this. They're the ones that actually give consent. So we're trying to figure out what a societal-appropriate risk would be for

children. We don't want research being done that carries excess risks to the kids, because we're trying to protect them. But it's the parents in the end, and that's come out time and time again, that are actually signing that consent form, not the kids. And they don't need to know risks and benefits to any of the research protocols that we do.

So I think the Goldilocks phenomenon, trying to get it perfect, we actually don't need to get it perfect, we need to get it adequate, and then let the parents decide if they're willing to take a risk for that study for their children. And I've done two studies where I thought they were reasonable, and I go to get consent, and I was completely unable to enroll kids into the studies, because when I presented the options, the parents go, "No, I think I'll just do this, thank you." And I respect that.

In San Diego, where we have the largest military concentration on the West Coast, with the Navy, submarines, the Marines, a Navy Air station, and when the premier of North Korea was on TV talking about his ballistic missiles, and there was a map behind him, San Diego was one the targets, which wasn't lost on us. But in terms of looking at risk, and you brought up this rural versus city, we believe that San Diego is a high-value target for a bio-terror attack. So families in San Diego, I believe, a parent would be more likely to accept a study than a

parent in rural Montana. So we need to make sure that the risk of the step is acceptable; I'm not trying to get away from that. But for a parent in San Diego, who is aware of the some of the Navy's exercises and maybe one of the Navy families; for a parent who wants to be part of the anthrax trial or a vaccine to protect their child, and that's a judgment.

So I'm moving the bar one step further, it's not just a responsible parent, it's a good parent who wants to be in a study to protect their child. I think the parent needs to be even one step further in the discussion than you've gone, as opposed to the charitable thing. I think the parents' concerns for protecting their children from such an event need to be considered. And that's another whole sticky wicket. And I recognize that, but I wanted to put that on the table.

DR. DEGRAZIA: Well, you've reminded us that parental, I use the term "permission," I tend to use "permission" instead of "consent" because it's sort of different from a grown-up deciding for him or herself. Parental permission is a necessary condition. And fortunately, we don't leave it only up to the parents; we, society, or biomedicine, or whatever, has to decide what options can we, in good conscience, present to parents? Because some might be willing, for whatever reasons, to allow their kids to assume too much risk, or they may not be aware that there are alternatives that are much less risky, but just

as good scientifically. So, the parents, the child, the possibility of dissent and assent, the final decision-makers. Thank you. I'm not sure if there's any other questions I should answer.

MALE SPEAKER: No, no. Thank you.

DR. NELSON: Well, actually, John touched on my point. I just wanted to make it a point to ask you to the extent that which this reasonable parent standard was open to the possibility that there may be different ways and different groups of parents need to find what's reasonable, particularly if you've instituted a dispositional, deliberate approach to making a very decision about that. And I think the example of John gave was one possibility, where there could be a group of parents who think it might be very reasonable to enroll their child, where another group of parents did not perceive the risk in the same way would think it's unreasonable. I don't have the answer to that question, it just raises an interesting further evolution of this notion of reasonable parenting. It's that sort of operational or normative ideal.

DR. DEGRAZIA: Right. It might. And as I say, I haven't tested out these ideas that much. And I'm not sure where it would lead. If it turned out that there were enormous ranges in risks that parents would allow for their children, I might get nervous and say, "Hey, let's stick with the relatively

minor idea. Because I'm pretty sure that children can't give informed consent." There are limits to how much risk that it should be possible to have them undergo unless there's a prospect of direct benefit. And you could even then go to a completely different notion of never using them as mere means to societal ends, as a way of trying to strengthen some ceiling there. And that's another discussion.

CHAIRMAN BOTKIN: Dr. Glantz.

DR. GLANTZ: Well, thank you for that thoughtful discussion. First my thought is I agree with you, there's no obligation to be a search subject, by the way, for adults or children, but that's for another discussion.

I want to pick back on something that Norm said. He talked about battery; of course, he's a lawyer on TV, as you know. But it seems to me that there's a difference, a distinct difference between what parents let their children do, with their child-like things, like shovels snow, or ride their bike, and a doctor putting a needle in someone's back because it's just like riding a bike. And it seems like it's not just like riding a bike, that even if, you know, in some ways you can come up with quantitatable risks, then that's not a child-like thing. And so once you say, we let parents agree to let their kids play high school football, therefore you can whatever you want, to kid, because there's nothing like that in medicine.

DR. DEGRAZIA: I actually wouldn't accept that example. And I'll tell you why.

DR. GLANTZ: Okay. But the question of what do we do to kids, as doctors, or researchers, or parents, strikes me as quite different to what we permit kids to do.

DR. DEGRAZIA: It does. You're right that they seem different. But there's still a question, are they different in a way that's morally relevant? Does it matter that a doctor is performing an action and putting an injection --

DR. GLANTZ: But it's not a child-like thing. It's not something that the child sees happen, like riding a bike or shoveling snow, or doing things like this. It's a qualitatively different thing. But let me move on to another point, because we have limited time.

I didn't understand your position that you shouldn't force kids to be research subjects. Because you pointed out that if you force kids to go to the restaurant when kids don't want to go the restaurant, we force kids to go to their room, we force kids to go to summer camp when they don't want to go to summer camp; so these are all kid-like things. It seems to me that there's no moral distinction putting a needle in the back. It seems like parents should be able to force their kids to do it since we let their parents force their kid to do all these other things that they don't want to do.

DR. DEGRAZIA: Well, in the case of forcing a reluctant child to go to a restaurant, part of the justification there is that the parents really want to go to the restaurant, and they can't leave their child at home. And I take it you would agree with me that that's okay, even though it's not a perfect maximization of the child's welfare.

DR. GLANTZ: Oh, I think we force kids to do stuff all the time.

DR. DEGRAZIA: And it's okay, right?

DR. GLANTZ: Yes, and it's okay, and that's why I think you would conclude, therefore, that you should be allowed to force them to be a research subject.

DR. DEGRAZIA: Oh, I see. And that seems --

OPERATOR: -- is now joining.

DR. DEGRAZIA: And so the question was why --

DR. GLANTZ: Well, see, you're the one who thinks that parents shouldn't be able to force kids to be research --

DR. DEGRAZIA: Yes, I think they should not be able to.

DR. GLANTZ: Well, that's what I'm -- so, that's all right.

DR. DEGRAZIA: Yeah. Let me think. It seems to me, intuitively, there's a big, relevant difference between parents making the kid come to the restaurant, and parents making their

kid enroll in a trial. And I don't have my finger on the relevant difference. If you know what it is, please tell me.

DR. GLANTZ: Well, I think one is that we're doing something --

DR. DEGRAZIA: More in an institutional context.

DR. GLANTZ: -- which is not kid-like, which is putting them a needle in their back, and the other is telling your kids, "You're going to have dinner with your parents." And I think that this the difference. And I would hope that there's a different between putting a needle in someone's back and having dinner with their parents.

DR. DEGRAZIA: But even if there's no needle in the back, even if it's just a questionnaire and the kid really doesn't want to do it for some reason, I think that would be sufficient for not making the kid do it. So it doesn't have to be a needle in the back. That'd be painful. I mean, that just it makes it more --

CHAIRMAN BOTKIN: All right, let's take one last question.

DR. WILFOND: Sure, I'll be brief. I can't help but make just a really quick comment: I have a nephew who I'm pretty confident would much rather have a needle in his arm than get on a bicycle, but that's beside the point.

David, I'll be really quick, it was really more of just a clarification about the reasonable parent idea. I just wanted to draw up two other modifying words that you were applying a couple of times. When you were talking about the lower threshold, that we don't expect parents to do everything in the child's interest, that strikes me as being more like acceptable parenting, so we have a lower threshold of acceptable parenting that might be below reasonable parenting.

And then also, Loretta mentioned the idea of the scrupulous parent, which is really a metaphor that Benjamin Friedman used years ago in his paper that was really meant to describe the IRB regulations, and how IRBs ought to be functioning as scrupulous parents. And I didn't know whether, in your choice of the word "responsible parent," whether you were being intentional in using a distinguishing word, whether you thought it was interchangeable, or whether you meant something different by them.

DR. DEGRAZIA: Yes, I didn't use reasonable, I did use responsible.

DR. WILFOND: Oh, I'm sorry. I was meaning responsible.

DR. DEGRAZIA: Yes, that's okay. Yes. I did responsible.

DR. WILFOND: Or scrupulous.

DR. DEGRAZIA: Scrupulous, I like that. But it sounds slightly stricter. And then the other one was acceptable, this sort of minimally acceptable. We may be close to the grey area on that, I'm not sure. No, that's a good challenge. I need to think more carefully about which descriptor really captures what I think this is defensible, and what its implications are. "Minimally acceptable" sound a little scary to me. "Scrupulous" sounds pretty good, but on the other hand, the connotations are a little bit -- well, maybe I'll go with scrupulous. I don't know. But thank you for the challenge, I need to think about it more.

CHAIRMAN BOTKIN: Dr. DeGrazia, thanks very much for your discussion, and we've softened the ground a little bit for the next stage of our discussions. We have break now. Why don't we take less than half an hour, let's do 15 minutes, if that's conceivable, and plan on coming back at 3:40.

[Break]

DISCUSSION OF MINIMAL RISK

CHAIRMAN BOTKIN: Okay, so we've got a little bit less than two hours to address the minimal risk issues. Some of these are pretty familiar to us; we've been involved in this field for a while. Others a little bit less so. We've got five bullet points here of nested questions that we want to try to get through. At least from my perspective, I think we've got a half-day tomorrow and some of the particularly interesting issues for the second half of tomorrow morning, so I'd very much like to get through the minimal risk questions today and not have spillover so that we lose time for some of the particularly interesting questions that have been outlined for us.

So what I'll do: We have slides on each of the bullet points, and I'll go ahead and read the full bullet point, even though it has several questions within it, and then really open it up for discussion. Again, what we're looking for here is some element of consensus, as much as we can achieve, or at least well-articulated majority/minority opinions, et cetera, on these questions. So as folks speak to these issues, we want to try to have your comments be articulated in a way that comes to specific answers to the questions that have been posed for us.

So here's our first set of challenges. "The daily life standard is qualified by the phrase 'ordinarily encountered.' Ordinary can be understood to mean common, usual,

or normal. Should any activity of daily life (regardless of the associated risk) be considered when judging whether a research risk is minimal? Should activities of daily life with especially high or low associated risk be excluded? How should one decide which activities of daily life should be considered appropriate comparators when assessing whether research risks should be considered no more than minimal?" Dr. Kopelman. And I also still want folks to introduce themselves as they begin their comments, please.

DR. KOPELMAN: Loretta Kopelman. This, again, is the everyday standard is very ambiguous, and some of the problems that we've heard today go back to the inherent ambiguity of whether we're talking about all the risks ordinary people encounter, which, if you adopt that, would allow very high risks, firefighters, and police, and soldiers. We mean the risks all people ordinarily encounter, which is sort of like a basic denominator of risk. And how do you find that out? I think of the two, certainly it's better to use the risks all of us encounter, rather than the risks some of us encounter. But that, for children, is going to include some very common things, like bullying, and nightmares are very commonly encountered for all children, and yet those don't seem to be appropriate standards for risk.

So to my view, what is routinely faced, risks in everyday life is a very questionable standard to use, and in my view, the routine examination standard is a much more definite standard, a much clearer standard, and really includes every procedure the Institute of Medicine gave as an example of common research risk procedures categorized by minimal risk that would be covered.

CHAIRMAN BOTKIN: Is there any way to salvage the ordinarily encountered daily risk standard from your perspective? Is there a way to interpret that language that would narrow the spectrum of risk susceptibly?

DR. KOPELMAN: Well, I think David Wendler is trying hard, and I give him credit for that. But basically, you still have to say why you think this is a good measure. I mean, there's no way to argue that nightmares aren't part of the everyday life of most children. Almost all children have nightmares, bullying, and yet I wouldn't think that would be an appropriate standard for minimal risk.

CHAIRMAN BOTKIN: Is there general agreement that the daily life standard, as traditionally interpreted, would not include the higher risk activities that some children and adults engage in on a regular basis? Norm?

DR. FOST: Yeah, I mean, I agree with Loretta. It should be discarded. And I would add the reasons that I

mentioned before, and alluded to that there's a difference between allowing children to do things versus doing things to children, like sticking needles into them or in the back of their arms and committing what would otherwise be battery. And second, as has been pointed out, the risks of daily life are often compensated by benefits, like bike riding and playing, even playing football, and stuff like that.

And third, as Loretta said, just because some very bad things happen to you in life that have almost no compensating benefit, like nightmares, doesn't mean that it's okay to double that risk. Even if you had a 0.01 chance of having a nightmare in the year, it doesn't follow to increase that to 0.02 by exposing a child to a research study; you would want to keep the nightmares, or whatever the bad things are, as low as possible, and doing it for a research purpose doesn't justify it.

DR. GLANTZ: I think part of the question is how is it helpful; that if it went away, how would affect the deliberation of IRBs or others in determining what a risk is, particularly in the context of biomedical research, where it seems that an ordinary diagnostic or an ordinary physical exam is much more analogous to what happens to kids in biomedical research than the risks of daily life? I just don't see how it adds a level of protection, or even if, in anyone's experience, has it added a level of protection?

CHAIRMAN BOTKIN: I think the level of analysis I'm guessing wasn't adequately anticipated at the time it was promulgated, and folks simply assumed everyday life has some low element of risk, so it was a way of articulating low when in fact it may well not be. Dr. Silber?

DR. SILBER: Yeah, my thought on that is that ordinary encountered can be qualified a little bit better, and then it gives us some guidance. For instance, I would have said ordinary encountered in a protected environment, and we all know what I mean by that. The kids that have the playground, and you put the rubber where they play instead of letting them fall on the earth. So all those things that we have in our civilization created that protect kids in their everyday life should be part of the consideration of what is ordinary encountered.

CHAIRMAN BOTKIN: Dr. Bradley.

DR. BRADLEY: John Bradley. In one of the materials, the concept of minimal risk was broadened to include those of a routine medical pediatric office visit, and that includes immunizations and occasional blood tests; not lumbar punctures, but other things. And as we look at medical research, I think it's much easier to compare risks that society accepts for immunizations and compare those with the types of studies that we're doing for drugs and new vaccines, as opposed to regular daily events like riding a bike. And most families who have

kids certainly have experienced routine office visits that are fairly well standardized by the American Academy of Pediatrics.

And I think those risks are fairly well defined. We know what each of the vaccine risks are that parents are willing to take, but they're willing to take them with the benefit that it's going to prevent diseases that are out there, which have morbidity, generally not mortality. And again, I'd like to make the case that medical countermeasures aren't designed to just injure people; it's designed to kill them, including children. So while I think I'm very happy to deal with minimal risk as it is defined by equivalent to a routine office visit. To take medical countermeasures out of the assessment of risk for other studies I think would be appropriate, simply because the consequences are so high with a medical countermeasure. And I think that that's the charge of our subgroup to look at medical countermeasure.

CHAIRMAN BOTKIN: I do, although I want to set that consideration aside for the moment and just deal more generically with the risk issues posed. And I think we'll see perhaps how that might change in the context of that particular research environment. Steve?

DR. JOFFE: So let me respond to the point that you just raised about whether vaccinations, which are obviously a part of routine pediatric care, belong in the set of comparative

risks that we should be thinking about. And say why I think you're mostly wrong, but there's an interesting sort of caveat to that that I think's worth exploring. So, in general, vaccines that kids get during routine office visits have some risks. In general, the reasons that we think it's appropriate for parents to accept those risks on behalf of their kids is because of the benefits that the kids get from being protected from those diseases that are out there in the environment.

So the sort of underlying rationale for why we accept vaccines in those situations is different to me than the rationale for why we might accept experimental vaccines in a vaccine trial. In particular, for diseases that are not, quote, "out there." The caveat that I find interesting is: So, if I had said when my kids came up for a vaccination, "Okay, I don't want them to get a polio vaccine, and I don't want them to get the diphtheria vaccine, because the likelihood that they will exposed to polio or diphtheria living in the United States is just remote." I wouldn't have been harming my kids. I think the reason to keep those in there is because if we sort of relax vigilance around those vaccines, there's the concern that those diseases might start to come back.

So it's really a herd immunity kind of phenomenon that justifies our exposing our kids to the risk of those two vaccines in particular. And again, if a parent said, "I don't

want my kid to get those two vaccines," we wouldn't think they were being irresponsible with respect to their particular kids, although we might think that they were being irresponsible with respect to the community. So those two, to me, give me an interesting sort of analogy for sort of acceptance of the risks of vaccines, not for the benefit of the kid, him or herself, but for the benefit of others, the benefit of the community.

CHAIRMAN BOTKIN: Norm?

DR. FOST: Norm Fost. I don't know if it fits appropriately under this bullet, but since vaccines trials have come up, am I allowed to make a comment about the ethics? I want to talk particularly about the placebo controlled vaccine trials in which the claim is made that that's a non-beneficial intervention; that there's no way you can benefit from a placebo in a vaccine trial. And this is a disagreement Skip and I have had for decades, and I'm not claiming I'm right, but I just want to get it out on the table. I think to look at each arm of a study as potential beneficial or not is not appropriate; you have to consider the whole package of being in the study.

So if there's a vaccine trial that has a placebo control for a very bad disease and that gives you a 50 percent chance if the trial hits a home run of being protected from this disease, that's better than the zero percent chance you have of not being in the trial, and that that therefore is a potential

benefit. If we had to consider it arm by arm, then no placebo arm would ever be justified, and that's back to the wacky Helsinki prohibition of placebo controlled trials that have been now discredited.

CHAIRMAN BOTKIN: We really are going against the component analysis concept, and you want the risk to be assessed pre-randomization rather than post-randomization?

DR. FOST: Exactly.

CHAIRMAN BOTKIN: Yeah.

DR. GLANTZ: Well, it seems to me, perhaps, that Dr. Bradley has brought up the issue of what is in an ordinary pediatric visit or exam, and whether or not that includes vaccination. I'm not sure that what the drafters had in mind. I'm not sure they were talking about an intervention as much as an evaluation, but we may go down the road of what an ordinary pediatric visit is.

CHAIRMAN BOTKIN: Well, sort of parsing out the specific nature of different vaccines, would we say vaccinations that are currently in use are low-risk, and can we make a general characterization about that? I mean, parts of the physical exam might not always be considered low-risk. Sometimes you need to do a rectal exam, right? Would we consider that minimal risk? It might be arguable, but so

vaccines might be a comparator in the general category of risks that are low.

DR. FOST: Yeah, the approved, but sometimes in the early phases, approved vaccines were not low risk. So, for example, rubella vaccine, which, in my view, is very prematurely approved for preadolescents, turned out not to be low risk, and for that reason, I prohibited my kids from receiving it.

CHAIRMAN BOTKIN: We would base our assessment on our current understanding of risks that are potential comparators.

DR. FOST: But just because it's approved, I wouldn't jump to the conclusion that it's low risk. The approval process can be heavily politicized, like the HPV vaccine.

CHAIRMAN BOTKIN: All right. Loretta?

DR. KOPELMAN: Loretta Kopelman. I just want to underscore that the definition of minimal risk does not include pediatric. It's general, and the routine examination is not pediatric but general as the comparator. And I tried to look it up. I looked under Bright Futures. I looked under the Institute of Medicine discussion of this. They said it was imprecise, but it generally did include vaccinations, maybe blood draws for cholesterol. And it has a whole list of things here which, to me, seem, as a basis for comparison, quite like the sorts of things I've heard discussed about minimal risk or in IRBs.

CHAIRMAN BOTKIN: Dr. Celento?

MS. CELENTO: Amy Celento. I guess to the point, Jeff, about approved vaccines having minimal risk, there's a percentage of the population that would disagree with you wholeheartedly. And so, you know, I'm not sure that we can just unilaterally say that they're minimal risk if they've been approved and they've been around for 30 years. So I think sort of to your point, Norm, but also there're many people who refuse all vaccines for their children, because they believe they're very high risk. That's not my personal feeling, but I just want to speak to that.

CHAIRMAN BOTKIN: Yes, but that raises the question about whether risk is objective or whether it's in the eye of the beholder.

DR. FOST: Some people believe in the latter.

MS. CELENTO: I agree with your comment. I'm just saying if we're looking across the board, and in going back to the point of responsible or scrupulous parents, those people feel that they're incredibly responsible, and I respect that. So, we have a lot of things here that could go either way.

CHAIRMAN BOTKIN: Well, let me just see if I understand where we're going with the comments so far. I think there's been agreement with Dr. Kopelman's analysis that the daily life criterion is too ambiguous, and that perhaps a better

one is the routine examination standard. So I think we're exploring what elements of routine examination make us more or less comfortable as fitting within an acceptable risk category. That's sort of what I see as the discussion here, and folks raised the question about, "Okay, daily examinations for kids include vaccinations. Is vaccination of accepted vaccines within acceptable risk range for the kinds of research we're talking about?" I think I have Steven next.

DR. JOFFE: So just a couple of caveats. I mean, I'd be hesitant conclude, and I realize there's not going to be any voting during this meeting, but I think the topic of whether the risks of routine vaccines can be sort of understood as being part of the package of performance of routine physical or psychological examinations or tests. It's a worthy one of discussion, but I wouldn't want to sort of jump too quickly to the conclusion that it should be viewed as part of that package.

My second comment is, I would want to think about if one dropped the daily life part of the standard, I would want to think about the implications for socio behavioral or non-biomedical research. It gives the definition a very biomedical sort of cast, and I'd want to think about it whether there's some kinds of socio behavioral research that our intuitions tell us may not be minimal risk, and yet wouldn't be well captured by that standard.

CHAIRMAN BOTKIN: All right, so taken as a given at this point that at least the vaccine part of the routine examination is met with some level of discomfort. Dr. Krug?

DR. KRUG: Yeah, I say this at the risk of complicating the discussion, and if I do, I apologize. But to the point about what's the average day, what's the average human, and what's the average exam, because it doesn't specify primary care or well-child care. Again, there are close to 30 million emergency department visits that occur for children in the United States every year, and that's a daily occurrence. So in the routine life of otherwise healthy kids, especially kids with special healthcare needs, they receive emergency services for which care is generally consented for, where there are issues that are brought up in routine daily life, where there are meaningful discussions about meaningful interventions that pose meaningful risk. And I just wonder whether we should be losing sight of that.

CHAIRMAN BOTKIN: Who else have we got? Okay, Skip?

DR. NELSON: Just two comments, one historical. If you look at the National Commission's report, I don't think it's unambiguous with respect to how they viewed vaccines, because back in 1976 there were some routine vaccinations, but they used some of those routine vaccinations to illustrate the minimal risk definition and others to illustrate 50.54/407 reviews and

swine flu, and so they were all over the park. So I'm not sure you can necessarily conclude from that historical record that they had a view in their mind about where any given vaccine may fall. That's a debatable point we don't have to get into.

The second is, I would caution you to just discard the daily life. Now, I realize if you look at international regulations, all of them basically, with few exceptions, talk about routine examinations, and very few of them have the daily life. But we do, and we have to apply it. And the rest of the questions actually ask how better to interpret it in a narrow way so it's not subject to the problems that Loretta points out. So I would encourage you, rather than just tossing it, to help constrain its defects.

CHAIRMAN BOTKIN: Okay, Dr. Celento.

MS. CELENTO: Amy Celento. You know, as we're talking about this, I just am taking a slight step back and looking at the fact that an examination is one thing, a treatment is another. So I don't want to complicate this, but I do feel that each time we talk about vaccines, it's preventative care, but it's really a treatment. You're getting a shot, you're getting a needle, something's happening, it's not an examination, it's not an assessment; so I just feel that maybe we should consider that as well, that they are assessments versus actually treatments.

CHAIRMAN BOTKIN: Dr. Fost?

DR. FOST: I'm responding to Skip. Just because something's in the regulations doesn't mean we should figure out how to live with it. There're things in the regulations that are just flat out wrong. I mean, mistakes were made. I know they're generally a very useful guideline, but there are things in it that just were big mistakes, like the exclusion of brain-dead patients from IRB review. I mean, under the regulations you can go to an ICU with a brain-dead patient and do anything you want. You don't have to get consent from anybody, you don't need any IRB review; I don't think anybody thinks that's a sensible thing.

And similarly, the placebo exclusion of the declaration of Helsinki, which is not a regulation but a widely-accepted worldwide standard which a lot of us said for decades, which is crazy, and finally they backed off. So if something's in the regs that's wrong, groups like this, as others, like the secretary's advisory committee and so on should have said the same thing, we should recommend correcting it; not living with it.

CHAIRMAN BOTKIN: Well, that's actually a reasonable prospect in this day and age. But taking Skip at his suggestion, let's conduct an exercise in creative interpretation of the language that we're stuck with. So what do we want this

term, then, to mean? So I'm going to read the questions again and see if I have at least a sense of where we are with any tentative answers here. "Should any activity of daily life, regardless of the associated risk, be considered when judging whether a research risk is minimal?" I'll go on to ask: Should activities of daily life with especially high or low associated risks be excluded?

I think I've heard general consensus that if the daily life standard is to be used, it should be interpreted to exclude high risks that some children may be exposed to as part of their daily lives. I don't think we've articulated a more refined sense of exactly where that line ought to be drawn, but at least I'm hearing consensus that we don't find acceptable high levels of risk even though some kids ride in the back of pickup trucks or play football in 100 degree weather, that that doesn't make that acceptable from a research perspective. Leonard?

DR. GLANTZ: I agree with that, and I think that we could say the reason for that finding is because this is supposed to be about minimal risk. That the idea is supposed to be a description of low risk, not a description of high risk. The issue that I have is the suggestion that it would be the average life -- there was some language in here. It's not up there, is it? The average ordinary --

CHAIRMAN BOTKIN: Yes, we'll pick up on that in a second, but the notion would be, if we sort of blend everybody's risk we're somewhere in the middle of that bell curve?

DR. GLANTZ: Right, but I think the idea is that the purpose of the definition of minimal risk is to try to define what a low risk is, not try to define what a high risk is. I'm picking up on your point.

CHAIRMAN BOTKIN: I do think that's how folks want it interpreted when the definition was written.

DR. GRABENSTEIN: John Grabenstein. Just from the management literature, you're not talking about six sigma, because that would be way too risky. You're maybe talking about one sigma or the middle of the bell-shaped curve, right?

CHAIRMAN BOTKIN: Okay, let me read the final question here and see where we are with that one on this set. "How should one decide which activities of daily life should be considered appropriate comparators when assessing whether research risk should be considered no more than minimal?" So Dr. Silber, I think, had a comment about this that the activities of daily life of those individuals who are -- what was the term you used -- not -- I'm sorry?

DR. SILBER: Protected environment --

CHAIRMAN BOTKIN: Something along the more sedate --

DR. SILBER: Protected environment, yeah.

CHAIRMAN BOTKIN: Are we comfortable enough with this? Leonard?

DR. GLANTZ: Well, I think a protected environment -- I think of kids who are, like, in institutions for kids who are developmentally disabled. I think of that as a protected environment.

CHAIRMAN BOTKIN: Okay, so we have to search for a better term, but it sounds like there's at least reasonable consensus that we're dealing with the middle of the bell curve and the lower risk end, as opposed to the higher tail.

DR. KRUG: Does --

DR. BOTKIN: Dr. Krug?

DR. KRUG: Steve Krug. Does the concept of a "protected environment" -- is the assumption or maybe one of the key factors being the presence of that responsible parent?

CHAIRMAN BOTKIN: Well, I don't know. Do responsible parents allow their kids to play football?

DR. KRUG: Well, it depends on which responsible parent you're talking to. My children believe that they had a miserable life because they were children of a pediatrician, but --

[laughter]

There are apparently lots of responsible parents or folks who are viewed as responsible parents who allow their kids to play football, soccer, all sorts of funny things.

CHAIRMAN BOTKIN: Yeah, so at any rate, that--

DR. KRUG: I don't know.

CHAIRMAN BOTKIN: Loretta?

DR. KRUG: Just a suggestion.

DR. KOPELMAN: Loretta Kopelman. I'm reluctant to do this, but I guess you could add the words expected and acceptable. I think it makes it close to tautological, but at least --

CHAIRMAN BOTKIN: How'd that phrasing go then?

DR. KOPELMAN: It would be the risks that are expected and acceptable in a stable society. If you want to add that, that's what South Africa has: a stable society. That would bring it, I think, to minimal --

DR. GLANTZ: But that would include football, right?

DR. KOPELMAN: [affirmative]

DR. GLANTZ: That would include high school football?

CHAIRMAN BOTKIN: Well, let me say that --

DR. KOPELMAN: It's okay. I mean, I think that's okay. I mean, parents can say, "No, you're not playing football," but I mean it's just as they can say, "No, you're not going to be in this study."

DR. GLANTZ: I mean, no, the --

DR. KOPELMAN: I mean, I think the ballpark is okay.

DR. GLANTZ: But the point is, we justify allowing kids to play football, which has substantial risks, because there's a benefit to it. But having the risk of a cervical spine dislocation for a non-therapeutic study would be totally unacceptable, because there's not a compensating --

DR. KOPELMAN: You're absolutely right.

DR. GLANTZ: Huh?

DR. KOPELMAN: You're absolutely right.

CHAIRMAN BOTKIN: Yeah, and that may well be the key justification for focusing on those daily life activities on the lower end of the risk spectrum, because there are no compensatory benefits for the types of research we're talking about.

MS. CELENTO: Amy Celento. I guess, to the point of protected environment, you know, it's a very common term, child proofed, fire proofed, you know, all of these things. It's really have you child proofed the playground? Have you child proofed the house, the school, the doctor's office?

DR. JOFFE: So, this question, and I think my comment is most relevant to this set of questions or this bullet point, although it's not precisely asked by any of them. So, in general, why I'm supportive of this sort of universal standard

of minimal risk, right, that we don't say, "Well, there's, you know, one set of minimal risk standards that are applicable to kids who are living in protected safe environments, and another set that are applicable to kids who are living in dangerous sort of background conditions."

But I'm wondering a bit about this, particularly in the international context, where the situations of kids who are living in, quote, "protected safe environments" in a country like the United States might be very different than the situations of kids who are, let's say, living in farming or nomadic communities in a rural low-income country, right, where a 6-year-old might routinely be sent out for 24 hours at a time to sort of watch the sheep. And if I sent my 6-year-old out for 24 hours to watch the sheep, I'd be arrested for child neglect or child abuse. And yet this is sort of a routine part of social life in some places.

So I just want to raise the question of whether there might be some variability of how we think about minimal risk relative to the background conditions of kids, and when are the times to say, "These are standards that are the highest attainable or the most appropriate in this society. We used to encompass everybody in that society, but that we might not want to sort of transport them or export them to every possible set of situations." So I do think bringing the international

context into this daily life standard, where the variability of daily lives, if we look across all of the context across the globe, is so dramatic that to say there's only one appropriate standard that we have to apply to every child everywhere in the globe could potentially run us into trouble.

CHAIRMAN BOTKIN: Okay, so you want the risk to be low, but you would permit some cultural context for what low might mean? Okay. Skip?

DR. JOFFE: At least I'm raising that as a --

CHAIRMAN BOTKIN: Possibility.

DR. JOFFE: Something worthy of consideration.

CHAIRMAN BOTKIN: Yeah.

DR. NELSON: I was just going to suggest that during the discussion if people want to keep page three of the background document open in front of him. The reason to that is, these five bullet points are not linear, which is why you don't see one, two, three, four, and five. But there's some logic to them, which is you're sort of answering with second and third bullet points the questions that the first bullet raised. So for example, "Is the purpose for which children are exposed to risks morally relevant?" I hear Norm and Leonard saying, "Well, yes, obviously." So you might want to just keep those five bullet points in front of you, because they are related.

This is not a linear set of questions. So it might be helpful to do that.

CHAIRMAN BOTKIN: Well, I think we've squeezed the life out of the first set of questions here, so let's move on to the second. "Does adding the qualifier, quote, of 'average, healthy, normal children' to the application of the definition of minimal risk further narrow the range of daily life activities that would be considered appropriate comparators? Please comment on the ethical arguments (such as considerations of justice) used to support the use of this qualifier." So we're looking at the average healthy, normal children qualifier.

DR. FOST: Norm Fost. It doesn't help, because average normal children play football and get concussions. It doesn't follow that we could expose kids to concussions when there's no benefit.

CHAIRMAN BOTKIN: And I saw this qualifier mostly as helpful with the absolute rather than the relative standard here, in that we weren't looking at the daily life of kids who were sick who might be involved in the research protocol, that that was the double jeopardy circumstance that this was meant to preclude. Does that sound right?

DR. FOST: Yes.

CHAIRMAN BOTKIN: Dr. Krug?

DR. KRUG: Yeah, I concur. I think the concept of a normal child is arguably ill defined and arguably pejorative, and there are lots of seemingly average, seemingly healthy children who actually are not normal. And if that's the population that we ultimately have to take care of and there needs to be thoughtful research conducted on that population, then why would we single out just the normal kids?

CHAIRMAN BOTKIN: Loretta?

DR. KOPELMAN: Loretta Kopelman. I think, as I understand it, the point here is whether you'll have a different standard of minimal risk for children who live in rough neighborhoods, or war zones, or the Upper East side of Manhattan is safe, and if you take the D train, you go up to the Bronx where it's not safe. Would you have a different notion of minimal risk? And I think that would be wrong. It would be unfair, to use the justice argument, to single people out who are already at greater risk through no fault of their own or their environment, and subject them to higher risk and research.

CHAIRMAN BOTKIN: So I think the IOM, and SACHRP, and others have pretty uniformly adopted the absolute standard for minimal risk, which I think is what you're speaking to. Steve, just a minute ago, talked about potentially thinking about different cultural context here, but is there consensus among the group that we're sticking with the absolute standard here,

and at least with respect to this particular language serving a function to say we're not talking about the sick kids who might be enrolled, but we're talking about minimal risk for healthy children as being the standard?

DR. GLANTZ: So, can I ask: it seems like "average" and "normal" are tough ones, what average and normal is, but what about healthy? Debating that qualifier, how average and normal are normative. And first of all, all of the children are above average in --

CHAIRMAN BOTKIN: I'm sorry, what's your suggestion then? Are you saying --

DR. GLANTZ: I'm saying, would it help if we just did healthy?

CHAIRMAN BOTKIN: Yeah, forget the other terms --

DR. GLANTZ: Because you mentioned --

CHAIRMAN BOTKIN: We just want to talk about --

DR. GLANTZ: Instead of average and normal.

DR. FOST: No, because first of all, healthy children play football and that doesn't give us any guidance.

CHAIRMAN BOTKIN: Well, it may be that that's a separate problem that we, to some extent, have talked about with that first set of bullets, but I'm wondering whether the inclusion of the terms average and normal was an ineffective way of trying to say, "We're not talking about the kids who are

playing football in 100 degrees. We're not talking about the kids in the back of a pickup truck. We're talking about the much more typical, perhaps, experience." And again, I don't think it works for that, but was this terminology trying to do two things: one, have the absolute standard be the appropriate standard plus limit the risk to the middle or the bottom half of the curve rather than the top half of the normal curve? Steve?

DR. JOFFE: Steve Joffe. So I realize Skip wants us to work within the regulations, but it strikes me that if we didn't have to use the heuristic of daily life to try to figure out what was more or less minimal risk, then we wouldn't have to get into this tortured conversation about whether you need this qualifier. And we could just talk about, "Okay, these sorts of risks are acceptable for, or here are some examples." Let's be casuistic about, "Here're some examples. Now work from these examples." These sorts of risks are acceptable for kids who are potentially participating in non-therapeutic research and these sorts are acceptable, and not have to use the heuristics of daily life. Then we wouldn't be having to have this conversation about the second bullet.

CHAIRMAN BOTKIN: Yes.

DR. NELSON: But Steve, as a practical matter, having been on the Institute of Medicine committee, and if I recall the Loretta, you were there too, this language was picked because we

wanted to lump everything together. I mean, it wasn't because we were thinking in these terms. But part of the difference is, with an understanding about how best to apply this interpretation, one can do that tomorrow. If what you're saying is we need to change the regulations, I'm not sure when that would happen. So there's a big difference between advice given today that's useful tomorrow, versus let's change the definition of minimal risk -- which certainly can be on the table, I'm not arguing against that -- which would take years.

DR. DAUM: I'm sort of debating whether I should make one or not. I mean, I've been in a number of conversations to try and define this term, and I'm despairing that there's probably very little that everybody around this table would agree with and call it minimal risk. Sort of left with a little bit like trying to pornography in hearing someone say, "I know it when I see it," and the minimal risk comes to the same kind of thing. I mean, what is average, what is normal, what is healthy, what is minimal? Is reviewing someone's chart minimal? Can we agree on that? We couldn't agree on giving routine immunizations in a doctor's office. So I'm just despairing that to try and get closer to a definition that everyone concurs with is not a productive use of time.

CHAIRMAN BOTKIN: Well, it's maybe a circumstance in which the original term has more meaning than the definition,

because it's the definition, the comparator that we're struggling with, as opposed to the notion that the risk should be minimal. Right --

DR. NELSON: Perhaps you hit the nail on the head.

DR. KOPELMAN: I think the least worst interpretation of the daily risk is the risks all of us encounter. I mean, that's the least worst. You know, and then you can be refined from there. The least worst of the routine examination, which is not targeted specifically to children, is the exams that are common to all of us too, and there you can get really, I think, according to the Institute of Medicine, you can get everything on their list in. So that transforms it to a uniform or absolute standard from a relative standard, which is problematic for the reasons we've talked about.

DR. FOST: Response to Skip's question about we have to figure out what to do tomorrow, because changing the regs would take a long time. Tomorrow, whatever decisions you or anybody else has to make, has to answer two questions: is this permissible within the regulations; and two, is it ethically permissible? And just because it's permissible within the regulations doesn't mean it's ethically permissible. So a study tomorrow that's asking about a non-therapeutic study that has a one in a thousand risk of concussions, yes, that's permissible within the regs. But I hope no IRB or FDA committee would

approve it. This is an ethics subcommittee, and the advice, at least as I'm hearing it, is to not use that standard tomorrow, because it may be acceptable from a regulatory standpoint, but ethically, it's problematic.

CHAIRMAN BOTKIN: Skip, do you want to respond?

DR. NELSON: Norm, we're not disagreeing, with all due respect, okay? Right now we would say that that risk would be inappropriate under the current definition of minimal risk for a concussion in a minimal risk study. So I think you're really creating a straw man that is of not much use at this point.

CHAIRMAN BOTKIN: Dr. Bradley?

DR. BRADLEY: John Bradley. In trying to pull all of this together and using the daily life wording, it seems as though people have struggled with this issue earlier. And on page 125 of the Institute of Medicine report, they both quote the National Commission from 1977, as well as talking about the National Human Research Protection's Advisory Committee, which discussed this in 2002, and in their report in 2004. And they use the examination and immunizations routine as a way to take daily life and put it more in a research context. And they specifically state that, in addition to physical examinations and psychological tests, immunization, modest changes in diet or schedule, and non-invasive physiologic monitoring be considered as part of daily life. And I wasn't there in the discussions,

I'm not an ethicist, but that makes some sense to me. And knowing that the way that current immunization schedules are formed is in a very open, transparent way, the Advisory Committee on Immunization Practices, which is not a close committee, sponsored by the CDC and HHS, basically discussed all of the risks and benefits of vaccine. There's wide-spread discussion. The Academy of Pediatrics does the same thing, so the two are now in harmony.

So it seems as though we can get as close as we can to a public acceptance of risk with injections, as you point out, because that is different than an exam. And I think as we look towards research, and what risks would we accept and do we think the public accepts from research, that this is probably as close as we can get. So I think we can have daily life and research risks together if we integrate them in this way.

CHAIRMAN BOTKIN: Okay, no further comments here? Let me see if we have a general agreement. I'm not sure it's too much different than the first set of bullets, but I think we're looking at the qualifiers average, healthy, normal children as perhaps meaning, or should be interpreted to mean, primarily healthy children as a way of addressing the absolute versus the relative standard, and we're reaffirming our support of the absolute standard of minimal risk, and that further argument to discuss the need for interpreting the daily life standard as

being perhaps a homogenized daily life, or a randomly selected person within the population, or some interpretation that means on the safer side of the full spectrum of daily life risks that children and adults would be exposed to. Any further thoughts about that characterization?

DR. KRUG: The general pediatric population?

CHAIRMAN BOTKIN: I'm sorry?

DR. KRUG: This is Steve Krug. The general pediatric population, the pediatric population at large? Again, the point that we're trying to make here is that we're not talking about creating a risk scenario that reflects a comparative risk to children who have received a bone marrow transplant for leukemia, as an example. So we're talking about the population at large, which within it has kids with asthma, there are kids with attention deficit disorders, and various other things; kids live in good neighborhoods and bad neighborhoods; kids who play football; kids who don't play football. That's what we're really talking about.

CHAIRMAN BOTKIN: Yes, I think we're in agreement. Skip?

DR. NELSON: I guess I would wonder if you are in agreement. The Presidential Commission, not the current Presidential Commission for the Study of Bioethical Issues, but the one back in 1978 to 1983, I think it was, made a similar

kind of recommendation. It might have been the most recent one where they talked about the general population. And so they basically took all of the risks across diseased groups and non-diseased groups to argue that that, then, would be the way to interpret minimal risk. And I think this definition of healthy says that's not, in fact, what you should do. So what you just proposed is not what the Institute of Medicine proposed in saying it should be healthy children; that the risks of minimal risks should be the healthy population; not a sum of all the risks across the entire pediatric population. So I would hesitate for people to think that that's saying the same thing, because that's in fact not saying the same thing.

DR. KRUG: You are correct, and that's --

DR. NELSON: So you may want to say that. I'm not --

DR. KRUG: No, I actually --

DR. NELSON: Disagreeing, but it's not the same thing.

DR. KRUG: No, thank you. So the point I'm trying to make, which I think I said before, is that we have to look at children as something broader than just the subpopulation of children who don't play football, who live in great neighborhoods, are incredibly healthy and at least average, if not, above average in terms of their school performance. It's about the general pediatric population. Yes, we should not drill down into a specific subpopulation of kids who face

horrible risks in their lives for a variety of reasons. And within that are children that are not just purely average or healthy. It's a little broader than that.

DR. GLANTZ: But then there's no definition of minimal risk. It's whatever happens to kids, or to kids who get shot and run over by, you know, buses and that sort of thing. The idea is to try to come up with an idea of what a minimal risk is, not what every risk is.

CHAIRMAN BOTKIN: I think we're in agreement here, even if we're struggling to find exactly the right terminology. I think that the consensus is that we're not talking about kids who are sick or perhaps the subject of the research because they're sick. It's not their daily life experience that's the comparator to make it minimal risk. The minimal risk is compared to kids in the general population, and I think what we want to say is it's on the safer side of that spectrum of risk that kids normally experience as part of their lives. But we have articulated exactly where that line is. We understand that kids in daily life have a spectrum of risk, and they have a spectrum of risk because some kids are sick. But nevertheless, the acceptable risk I think we're trying to articulate is on that safer side of that normal experience. Anybody else before we move on to this next set? All right.

DR. DAUM: Can I go out just as an agnostic?

CHAIRMAN BOTKIN: Sure.

DR. DAUM: At least in the sense that I hear the point that Skip is trying to make, and I think it's an important one. And I think you could take a population of bone marrow transplant children and propose a study to review their medical records about something, and it'd be minimal risk. And so it's not just an absolute about what the child experiences as part of their normal repertoire. It's a conglomerate, and it's a very difficult concept, and I'm not sure we've nailed it.

CHAIRMAN BOTKIN: Agreed. Third bullet, then: "Is the purpose for which children are exposed to risks morally relevant? In other words, is it equally appropriate to expose children to risks inherent in a 'research' activity versus a 'daily life' activity if the activities have comparable risks? For example, many life activities, like playing team sports, are enjoyable for the child (and they may teach discipline, teamwork, promote fitness, et cetera) in contrast to most research activities. Are there factors other than risk that ought to be considered when deciding whether daily life risks and research risks are appropriate comparators?"

And I think we've had already a fair amount of conversation with this. Both Norm and Linda I think spoke to the difference between children doing things and things being

done to children. So let's build on that conversation and see what other thoughts folks have. Ben?

DR. WILFOND: Well, a couple of things: I do think that the purpose is not necessarily irrelevant, but the question is what's the right comparison? I think this is where Dave's idea that charitable contribution standards might be useful, because it's an example of an activity that we do for the benefit of others that research is also like. So I think perhaps the question that we should be asking here would be, what are the types of risks that are acceptable for the benefit of others? It could be for research; it could be for non-research purposes as well. So I guess I wanted to reframe the question. And I'm not sure if that's helpful to you, Skip, or not, or whether it's important to keep it focused on daily activities.

DR. NELSON: You're welcome to frame it. Let me respond by actually poking Norm again. You know, in Wisconsin, having been there for 10 years, as Norm knows, and he's still there as an IRB chair for 37 years, plenty of parents have their kids operating farm vehicles. And presumably, are not hauled into court for child abuse or neglect based on injuries that might happen to those children using farm implements. I can recall a couple of years ago watching a special on, I think it was ABC News on ATV rodeos, with parents having their six and 7-

year-old kids jumping various obstacles in the four-wheeled ATVs, and segued right from that to a kid in a wheelchair who was paraplegic from having had the ATV turn over on him.

I mean, those are activities of daily life that we let parents make decisions to enroll their children, and we don't hold them legally accountable from the standpoint of child neglect to do that. But what is it that allows us to say that that's an inappropriate level of risk to expose a child to in research? I mean, I'm agreeing with that as a conclusion. My question is, what's the logic there? And what I'm hearing, and I guess my question is, is this what you've been saying for 37 years, because you want to just throw out the daily life thing and be done with it. But I'm assuming for 37 years you've had to come up with a different answer, because you're stuck with the daily life things. So what is it when investigators do that? I'm just curious.

DR. FOST: Well, a) we're not stuck with the daily life thing. As I said the regs tell us what we may do, but it doesn't tell us what we ought to do, and just because the regs say you can expose a child to a non-beneficial research study that has the same risk as playing football or driving a tractor, that doesn't mean you ought to do it or that an IRB should allow you to do it. It just says if an IRB does that; rightly or wrongly, they're consistent with the regs. The regs allow IRBs

too much latitude in that regard, and that's why nearly everyone who has spoken has thought the daily life thing is not a good standard.

Secondly, the tractor example, which is a good one, has compensating benefits. I mean, children are learning. First of all, it's tremendous fun.

[laughter]

Kids want to do it. They beg to be able to drive the tractor; whether it's in their interest or not, we could talk about. They learn farming. It has the charitable contribution, so it has lots of benefits. So that's why we don't report it as neglect. Although, if we had a 2-year-old driving a tractor and it tipped over, I think we might express some concern about the parents' judgment and whether they needed some supervision.

I just want to say something else about the charitable activity analogy, which I think is a good one, because I think that's very close to what we're doing when we put kids into non-therapeutic studies, but it's not sufficient, because you could have kids doing charitable activities that are just way too risky.

You tell your 3-year-old, "Junior, get in the tractor, and go down to the Red Cross, and help them draw blood," you know? Just because it's charitable doesn't mean we should allow

it. So that's why we still need some objective standard of risk, not just whether it's charitable or not.

CHAIRMAN BOTKIN: Steve?

DR. JOFFE: Steve Joffe. So what this discussion is telling me is that we have some intuitive sense of what is or what is not minimal risk, and when we hear about a parent allowing their kid to do some activity in daily life, set aside research, we ask the question, is that activity that this parent is allowing their kid to do that we as a society are not preventing them from allowing their kid to do, is that a minimal risk activity? So, is allowing you kid to participate in high school football a minimal risk activity? Well, I think many of us would say, "No, it's not." This doesn't mean we're going to stop parents from allowing their kids to do that, but there're some things that we legitimately allow our kids to do in the course of their daily lives that are greater than minimal risk.

Which again goes back to the point that we seem to have a standard in our minds of what is or is not a minimal risk standard, and we use daily life as kind of a rough first approximation to help us wade through that. But then when you start to really dig into it, you run into all the problems that we're running into.

CHAIRMAN BOTKIN: All right, so here's one way to think about it: One is that daily life activities have two

aspects of them that are different than a research context. One is the compensatory or the competing benefits. Kids get to do stuff, presumably, because things like football teach a lot of good things to kids, and that those compensate, arguably, for the risks. And then secondly, we have a much broader respect for parental decision making authority than we do for what's a socially sanctioned research intervention. In other words, we wouldn't intervene on parents because we respect their ability to make mistakes. Even though we may not think their decisions are wise, we don't step in to countermand those. Whereas, in a research context, it's a much more social environment where we have to have a clearer justification for what it is that we're exposing children to, and that that would argue for a more conservative level of risk than what we would permit parents otherwise to do on their own. Norm?

DR. FOST: That's well put, but I would add one thing to it. First, there's a tollgate for research activities. You have to go through an IRB. There's not a tollgate for all the billions of things that parents do for a good reasons, that there're not enough IRBs in the world to do that. Maybe if there were a tollgate, if you had to get approval to let your kid drive the car, or drive the tractor, or do lots of other things, there may be many things that would not get approved. But constructing the world in that way is just not feasible, and

the reason there's a tollgate in research is because of historical errors that were made. I mean, things that doctors and parents, left to their own, just did really wacky things. Now, that happens in parenting, too. That's why we have a million-plus reported cases of child abuse a year, which is only the tip of the iceberg, but it's very hard to get a prospective review of parents' decisions to beat up their children.

[laughter]

DR. GLANTZ: So I think one of the things that makes a difference, again, is that we're producing the risks, but the question of who the "we" is matters. And so what we're asking is, what is inappropriate for doctors to do to children? That's sort of a part of it, and one of the ways we try to do that is by thinking about why doctors do things to kids and what the minimal risk is. So should physicians who are supposed to be loyal to the interests of children be subjecting to the equivalent of tractor pulling, or tractor driving, or whatever it is? And is that the role of a physician or a healthcare facility in order to derive benefit for somebody else? And I think that that's the context in which it happens. It's not the parent doing it; it's physicians and healthcare institutions doing it, and that's different.

CHAIRMAN BOTKINS: Steve.

DR. JOFFE: I just wanted to respond or at least add on to what Norm said a moment ago. So I think the reason that we don't police these decisions that parents make in the course of their ordinary family lives is in part because it's not practical to do that, but in part because we believe that there's a zone of family privacy, and we respect families' rights to make the sorts of decisions that they view as consistent with their values, and their own interests, et cetera. As soon as we start to move into the research realm, it's not simply a matter of family privacy anymore; it's also a matter of the fact that we're implicating professionals, professionalism, institution sponsors, and government. There's a whole bunch more stuff of actors that are implicated in that decision. And so we police that because of all the other players and not because it's merely a matter of family privacy.

The one other consideration I think is relevant is that we recognize that people who are deciding about their own participation in research and parents deciding about their children's participation in research are not perfect decision makers. And so we want to sort of create some safeguards around what it is that we will or will not offer to parents, offer to families, because we recognize that if parents were perfect decision makers, I suspect we might be willing to get that broader in what we were willing to offer. But we want to have

some fairly tight safeguards because of the possibility that parents are going to make mistakes in the sorts of things that they authorize for their kids.

CHAIRMAN BOTKIN: Dr. Krug?

DR. KRUG: Hi, Steve Krug. Yeah, I actually was going to say something similar to what the other Steve -- I'm the other Steve -- just said. I think in our society we allow adults to choose to do almost anything; not quite everything, but almost anything. And we then also allow adults who we perceive as responsible parents to make decisions on behalf of their kids: both decisions that relate to day-to-day activities, like should you be doing this, but also as a care provider, when I'm treating patients and I have to do something outside of the ordinary, I need the parents' consent. I can't do it without the parents' consent. I can go to the court and force the parent to do something that the parent is neglecting to do which will ultimately harm the child, but easier said than done.

And that has to apply to this process as well. I think we have to, within reason, expect parents to make reasonably good decisions that are appropriately informed. So first of all, this is very different than signing up for junior football. There's an IRB that defines a process here that's looking at merit, that's looking at risk, that's looking at a variety of issues, and the IRB process may not be perfect, and

as Jeff pointed out, different IRBs will view the same question or issue differently, but that's the best we've got. And then I think you layer on top of that the well-informed decision by a responsible parent.

CHAIRMAN BOTKIN: Well, we're not talking much about the consent and assent pieces of the equation here, but it's a good point. What we're really talking about here is what risks do we sanction being offered to parents, because then there's that second stage where parents themselves have independent authority. So we're not necessarily talking about what risks do we expose children to, but what risks do we allow parents to be offered the opportunity to --

DR. KRUG: Well, let's --

CHAIRMAN BOTKIN: Consent on behalf of their kids.

DR. KRUG: So, good point. So unless we're going to stop allowing parents to sign up their kids for tractor pulls or football, we have to allow parents to make well-informed decisions regarding an IRB-approved protocol, some that pose no risk, like, "Look at your kids' chart," to some that actually might pose risk: "I'm going to give your kid a shot which could cause an interesting" -- and you can decide, because you live in San Diego that you're worried about somebody dusting your city, so you can say yes or no. I think we need to allow parents to

make those decisions. They've been making those decisions for decades, centuries.

DR. FOST: This is an attempt to synthesize your last comment, and Len's, and Steve Joffe's, that we've been talking about is about what parents may do in ordinary life and what they may do in a research setting, but that's not the right parameter. What we're really discussing about today is what investigators may offer parents, and what IRBs and funding agencies may approve. That is, if we're saying it's wrong for an investigator to propose a study in which the risks are comparable to, and a non-beneficial study, and that has risks comparable to things on the high end of daily life, he or she should not be allowed to do that, so parents shouldn't be put in the position of having to make that decision.

DR. O'LONERGAN: So as far as daily life, there's lots of things we don't let parents do. I used to ride dressage and I used to do it without a helmet, and sometimes I fell off, and sometimes it didn't go well. But now, in order for girls to compete in these kind of competitions, they have to have certain certified kinds of helmets. We don't let parents make those decisions. If your child's going to perform in this competition they have to have certain kinds of helmets that they wear. Other kinds of protective gear; we make parents put kids in seat belts, so we don't leave them an option. So this is not that

different. The IRB is saying there are options we won't allow parents to choose from. Does that make sense?

CHAIRMAN BOTKIN: And that's because we, as a society, think that the benefits of riding without a helmet aren't sufficient to justify the risks. But we allow them to enroll their kids on football teams because we think the benefits of football outweigh the risks of football, or at least arguably so that parents are making reasonable decisions if they would do so.

DR. O'LONERGAN: We still put helmets on.

CHAIRMAN BOTKIN: Yeah. All right. Have we answered the questions? So are these other aspects of daily life activities, in other words, the benefits and the spear of parental authority, do these make those risks different in the daily life context from the same level of risk, let's say, in the research context? And I think we've decided that we allow parents to let their kids play football given a certain element of risk. If we translate that same risk in terms of probability and severity into a research context, we might say "that exceeds acceptable threshold, because," and is that because there are no compensatory benefits in the research context, and so the risks are not equivalent? Even though we compare the risks to daily life, some daily life risks are unacceptable because they have other aspects to them that make them socially acceptable that

aren't present in a research context. Was that question too scrambled? Is that what we're saying? Skip?

DR. NELSON: Jeff, let me see if I could link together the next bullet point with some of the comments that have been made, and the next bullet point talks about this notion of the scrupulous parent. It talks about charitable participation, but talks about this notion of scrupulous parent, and I was interested in David DeGrazia's presentation of a reasonable parent. And let me make an attempt here to see where I think there could be a relationship.

So when I think of scrupulous parent or reasonable parent, I am not thinking of what an actual parent may decide, but more in the sort of normative idea and legal domain about what a reasonable patient would want to know in an informed consent process. In other words, it's not just what I as the physician thinks they should know. I mean, I should tell them that if I do, but it's not up to me. And it's not everything that that individual person wants to know, because I can't know that, but the legal standard I'm held to is this notion of the reasonable patient standard, that I need to inform them of what that reasonable patient would want to know.

Now, of course, if they ask me questions beyond that, I need to inform them. So I see it as some sort of normative ideal, or operational concept that helps structure what we think

about this notion of parenting. And so let me give you the football example, which I think is good. If one wanted to ask the question in a football game about what's the instance injury between the 140-pound safety and the 280-pound tackle when they collide? I mean, probably if you're sitting up in the stands watching, that would be okay. You're just watching the football game to see if that happens to happen, what will happen to the 140-pound safety when the 260-pound tackle hits that. But you wouldn't design a research study where they start at two different ends of 100-yard hallway and run into each other to see what that would happen. Even though the risk may be the same, you wouldn't use that as an argument. I personally think that's uncontroversial. I'll put that on the table as uncontroversial.

So what is it about the scrupulous parent that would say, "You know, in this you got to be crazy. You're going to line my kid there up and that big kid there and have them run into each other versus" -- it's all right. We'll have them go play football, and they may or may not run into each other. So I guess I try to articulate that difference around this notion of scrupulous parent. I think David was getting at perhaps that this notion of reasonable parenting, but not just the kinds of decisions that parents would make, but the sort of decisions we think parents ought to make in that kind of setting. It sort is

a normative ideal, a social concept. So I'll just leave it there.

DR. GLANTZ: But I think what's derived from that is that the focus on risk is not enough, right? That there were other things that go on? For some reason, the conversation, even the conversation about the support study and the hearing that was last week, is all about risk, and risk is not enough. We're talking about appropriate use of children for a particular purpose. So the question about the "Could you line up the 240-pound kid and the 140-pound kid in a hall and see what happens?" we shouldn't let investigators do that. It doesn't get to the point of a parent, and this is the point that Norm was making and Jeff was making because we would say, "That's an inappropriate use of children, and that's an abuse of the obligation to protect kids." And it doesn't just have to do with the risk. It's just not right, and that's a much hotter concept to get at, that it's just not right, that there is some normative standard that's violated by doing that, because the risk is the same. So there's something else that's going on.

DR. NELSON: No, I understand, and that's precisely what I'm trying to draw out, is what's not right about it, as opposed to just this gut intuition, and trying to somehow articulate that in a way that understands, because when I go back and look at the National Commission, I think their

definition of minimal risk was an attempt to capture this notion of responsible parent. And they gave a statistical definition, which has gotten us into this bind of talking about risk, but in reality it was meant to try and capture this domain of responsible parent.

DR. GLANTZ: Well, I think the problem of lining kids up in the hall is that they're doing it for me, right? They're not doing it for them. It's not sort of a spontaneous kid-like thing, and that the reason why they're doing it is because I put them there, and I'm interested in writing a paper about it, and that I'm using them to find out something, and that that's the problem that I think that makes it different than the football game itself.

CHAIRMAN BOTKIN: Well, let me push you on that, because I think kids crashing together is a very kid-like thing. So --

DR. GLANTZ: 140-pound kid and a 280-pound kid?

CHAIRMAN BOTKIN: But it is the risk that makes that unacceptable in the research context.

DR. GLANTZ: For us to create that risk.

CHAIRMAN BOTKIN: It's not the risk that makes it acceptable in other context, but in a research context it is the risk that makes that wrong, right?

DR. GLANTZ: [affirmative] It's --

CHAIRMAN BOTKIN: I mean, you get 280-pounders and put them three feet apart, and say, “Why don’t you guys bump bellies,” nobody would worry so much about that, right?

DR. GLANTZ: So I’m saying that the context of research makes a difference, because we’re using the kids as a means to an end, right? That’s the reason why I have my kids lining up, not to see who wins the football game; they’re not part of a larger recreational thing.

CHAIRMAN BOTKIN: But that is not in and of itself wrong; that’s the reason why we have to minimize the risk, right?

DR. GLANTZ: I understand. Yes, I’m --

CHAIRMAN BOTKIN: I mean, you’re not arguing that --

DR. GLANTZ: No, no, I’m with you.

CHAIRMAN BOTKIN: Right. Okay.

DR. GLANTZ: That’s exactly what I’m saying, because we shouldn’t be creating that risk and putting kids at that form of risk in order to help ourselves, that level of risk. I’m not talking 240-pound kids.

CHAIRMAN BOTKIN: Steve?

DR. JOFFE: So I want to respond directly to this bullet point here. So, for me, as I’ve thought about the sort of responsible parent or scrupulous parent standards, I haven’t really found in my own thinking today that it’s gotten me beyond

the issues of minimal risk. It almost seems like a rephrasing of the minimal risk criteria. And what sort of risks would a scrupulous parent allow their kid to be exposed to in research? Well, minimal risk. So just a restatement. So I'm finding that one less helpful.

The charitable participation one on the other hand, it certainly doesn't answer all the question, but I do think it gets us closer in the sense that it helps to clarify which subset of, quote, "activities of daily life" might be appropriate comparators. Again, it doesn't sort of totally fix this up, but it helps get us closer; at least eliminate some.

And finally, it's been pointed out a number of times that the definition of minimal risk doesn't specifically say, for kids, the daily life of children, or the daily life of children of comparable ages, or something like that. And yet, I think looking at these attempts to get more specificity around the standard, the minimal risk standard has to be interpreted as the daily life of a comparable class of individuals as opposed to the daily life of firefighters, or even the daily life of average healthy adults I think would be a problematic comparator if we're trying to decide what's minimal risk, for example, for a young child.

CHAIRMAN BOTKIN: Let me see first is there general agreement with that point that we're talking about sort of

class-specific risks and that it's certainly not appropriate to compare kids with soldiers in Afghanistan, but do we need to compare 1-year-olds with basically 1-year-olds, or a 1-year-old with a 5-year-old?

DR. GLANTZ: So class is not social class? You're talking about developmental class?

CHAIRMAN BOTKIN: So roughly the same developmental class, and sort of the experiences that a 1-year-old would have as part of daily life is the risk standard that we would pose in research for projects involving 1-year-olds. Is that the general concept? I've got a number of hands up here, but let me go with Norm first.

DR. FOST: Yeah, but I would add to it that it's the idiosyncratic 1-year-old also; that it should be patient or sort of research subject-specific. I mean, Jay Katz made this point 40 years ago that not all 50-year-olds are the same, and not all 1-year-olds are the same, so there ought to be some assessment, especially where there're psychosocial risks, where the risks are anxiety, or terror, or anger, or venipuncture studies. So there ought to be an assessment of the individual, not just because he or she's in the class of 1-year-olds that makes it okay. It doesn't mean it's okay for all 1-year-olds.

CHAIRMAN BOTKIN: Okay, so it'd be the level of risk that would be reflected in the daily lives of other children in that class?

DR. FROST: That's a necessary but not sufficient --

CHAIRMAN BOTKIN: Right.

DR. FOST: Necessary but not sufficient requirement.

CHAIRMAN BOTKIN: That's right. So 1-year-olds driving tractors wouldn't be able to...

DR. BRADLEY: John Bradley. There are two hurdles to clear here: one is, what is minimal risk to allow it to go through an IRB to go to the parents? So to use the example of the 260-pounder running down the hall at the 140-pounder, even though those risks would be similar to those in a football game, as Steve mentioned, there's no parent who would sign up for that; no reasonable parent, responsible parent, whatever term you'd like to have. But then when you start to parse it down: well, what if it's a 200-pounder against a 140? What if it's a 140-pounder against a 140-pounder? What if they're running not 100 feet down the hall: 50 feet, 30 feet, 20 feet? So the parent knows the child. So if this child is, for some reason, excessively worried about physical injury, then the responsible parent wouldn't let that child into the study even though the risks may be assumed by the greater public to be reasonable.

So again, establishing what a minimal risk is from the standpoint of what is okay to present to the parents, and then letting the parents take that next step to say, “Is this applicable to my child knowing from birth how my child’s reacted to these sorts of things?” And they can refuse even if we believe that the risks are reasonable, and we accept that, and that’s fine.

DR. KOPELMAN: Loretta Kopelman. Just to go back to the question, just to clarify, I think minimal risk is a standard to help decide the ethical permissibility of research; in this discussion, research with children. And I think both the charitable participation and the reasonable parent are excellent metaphors to help us. I don’t think they substitute for an analysis of minimal risk. Charitable participation doesn’t cover young children who can’t knowingly participate, and they grow up to abhor that they were in a study or not know about it, so it really doesn’t cover it. And the scrupulous parent, again, is a very helpful tool, but you owe us a definition of, when we disagree when it gets close, how you distinguish one from the other, and those very reasons are the reasons we need. So, I mean, while they’re both helpful, I don’t think they are fundamental.

CHAIRMAN BOTKIN: Well, let me go back to a question about whether the comparators are helpful. I mean, folks sort

of complain that there's no definition of a minor increase over minimal risk other than about that much more, right? So there's a circumstance in which we don't really have a comparator, but you leave it up to the judgment of the IRB to say, "Well, in this context I think that's acceptable or not acceptable. We're willing to shoehorn this into a minor increase over minimal risk." So I mean, I guess what I'm throwing out is whether we're continuing to create more problems by trying to find comparators that raise more questions than the original term itself, and might we just want to stick with minimal risk? And by minimal, we mean low. Just other terms that mean the same as minimal would be the definition, as opposed to saying it's just like something else.

DR. FOST: I just wanted to build on Loretta's comment that even the assumption that the child benefits from what the parent perceives of as charitable activities is not a certainty by a long shot, and there are two studies about this: Skip's is the most recent and the most robust, and not many people in the room are probably aware of him, but he did a fantastic study while in Wisconsin, and later in Philadelphia, of how kids, and I think you interviewed their parents also, on how they felt about being recruited into different kinds of studies. And if I'm remembering, there wasn't always a connect between there.

And the second individual whose name I can't remember, but it was a pediatrician in California who 20 years earlier did a similar study, not as well-designed as yours, but it mainly just interviews of kids, 7-, 8-, 9-, 10-year-olds who had been recruited into minimal risk studies on their parents say so.

And when you got them in a room by themself and asked them to talk about how they felt that their parents said it was okay to draw blood on them for research purposes, they said, "What? They did what, and you didn't ask me?" And they were under the illusion that this was just part of you're going to the doctor, and it was the therapeutic misconception. So charitable activity may be a helpful metaphor, as Loretta says, but it's not sufficient to go forward.

Skip, you should say something about those studies you did about how the kids -- am I remembering it right, that there was a disparity between the kids' and the parents' perceptions about it?

DR. NELSON: Yes, but I would say it was unfortunately anecdotal. I can't give numbers, but there was a disconnect between, often, children's participation and parents' views of that participation, yes.

CHAIRMAN BOTKIN: Let me see if I have consensus on this set of questions here, and maybe Loretta had what might be a good summary here, which is that the charitable participation

and scrupulous parent standards are helpful, and they sort of strike at some of the key issues we're trying to get at, but they're not replacements. They have their own sets of complexities and problems associated with them that wouldn't at this point allow us to jump to those as an alternative way of thinking about what acceptable standards of risk are.

DR. KOPELMAN: I would say they're illuminating metaphors, but whatever reason, they're not the basic definition or analysis.

CHAIRMAN BOTKIN: Not mature enough at this point.

DR. DAUM: So in listening to the discussion, I find myself a little confused and requesting clarification again. Whose definition? Who's defining terms here? So I like the analogy of the 140-pounder and the 280-pounder colliding. So it is the study designer that decides it's minimal risk, is it the IRB that decides the minimal risk, or is the parents that decide minimal risk?

DR. NELSON: The answer is the IRB.

DR. DAUM: So all this is about what we want the IRB to do?

CHAIRMAN BOTKIN: Yes. The investigator may well make a pitch to say, "I believe this is minimal risk. Therefore, it ought to be treated this way." But ultimately, it's the IRB that makes the call, and that's the threshold decision if the

IRB says, “Yes, it’s minimal risk.” Then it may go on to be offered to the parent, and the parent may disagree with that, not because they would disagree with the standard, but they would agree or disagree about whether the risk was acceptable or the project overall was acceptable as far as they were concerned.

DR. DAUM: So we keep talking about the parents agreeing or disagreeing, and we’re really talking about the IRB? I just want to clarify that.

DR. FOST: Well, there are many other tollgates besides the IRB. First of all, there’s the funding agency’s supposed to make judgments, the FDA if it’s an FDA-regulated agent, the FDA’s supposed to make judgments about this. There are data safety monitoring boards which increasingly see studies before they’re initiated, and there’re a lot of checks and balances in the system, but they all should be using the same interpretation.

MALE SPEAKER: And in that scenario, Norm, who decides?

DR. GLANTZ: The IRB --

DR. FOST: Each of them has to make an independent decision.

DR. GLANTZ: The IRB decides what is minimal risk under the regulations. Again, we’re acting as if the

regulations are the only thing, but they're the decider when it comes to interpreting the regulations.

DR. DAUM: They're not the only decider.

DR. GLANTZ: They're not. There're other people who could have an opinion.

MALE SPEAKER: Then what is the role of the IRB?

DR. GLANTZ: If the IRB says it's not minimal risk, it's not minimal risk. Well, you have to draw a distinction, and we keep failing to do that, between the individual subject and the appropriateness of the research. Those are two different things, right. Parents make decisions about their individual children's participation. We're talking about the acceptability of proving the research on an institutional level and those are different things. So the fact that an institution decides that it's okay to do something that is minimal risk doesn't mean that the parent has any obligation at all to participate.

Those regulations about minimal risk have nothing to do with parents. The parents can decide any way they want to. They're not subject to the regulations --

DR. DAUM: But we keep taking about it as if --

DR. GLANTZ: No. We're talking about it as a metaphor. So, if I said, "Should we just have an IRB of parents," if that's our standard is what the typical parent

would be then the IRB should be parents, and that would be how the decisions should be made or be, similar to a jury deciding what a reasonable parent would do. That's not why I asked to be called on though.

But I think that there is real problems with the charitable example, and because we seem to assume that there's no limit to what charities could be. So, Loretta talked about 2-year-olds don't do charity and 3-year-olds don't do charity, and the question of when a kid can be charitable and when they are moral actors is sort of up for grabs, I think. But the other thing is that charities have their own rules that, you know, you have to be 16 to give blood or 18 to give blood or something like that. The Red Cross doesn't take blood from 14-year-olds. Habitat for Humanity has rules about what kids can do. Five-year-olds don't get to hammer nails or saw wood. So, even if one says it's okay to do charity, it doesn't mean that charities are unregulated in terms of what is still acceptable for kids to do.

DR. WILFOND: Well, I just want to clarify, I think the whole idea of charity was not to set that upper threshold as just to say that at least some charitable things for the benefit of others are acceptable, not that all charitable acts are acceptable. I just want to be clear about that.

DR. GLANTZ: Right. And so, some charitable things are acceptable and some research with kids are acceptable. I don't think it gets us that far to agree on that.

DR. JOFFE: Steve Joffe, and just a very quick point. So, I don't think that referring to the charitable participation standard requires that the child be -- in other words, we're saying it's acceptable for children to be exposed to certain types of risks to benefit others. I don't think it's a necessary part of the thinking, and this is a direct response to Len's comment a moment ago, that the child has actually accepted his or her participation in activity, accepted those risks for him or himself. In other words, I think we could envision that there're certain types of risks that, say, a 10-year-old doing some sort of charitable activity might be exposed to that we judge to be acceptable that we might be willing to accept for younger children participating in research even though those younger children might not participate in the same charitable activity because they might be too young.

Now, I still think the thing that we talked about 15 minutes or so about the fact that minimal risk standard might vary according to what's a typical activity for a 1-year-old versus a teenager, I still think that holds and sort of constrains this debate. But at the same time, I don't think it's a necessary feature that we could only use the charitable

standard for kids who are of the age where it's appropriate for them to participate in charitable activities, at least in part by their own choice.

DR. NELSON: Jeff, I was just hoping there be a little bit of discussion, Steve sort of alluded to it, on the bullet point five, which gets at age, partly because I've heard some proposals that minimal risk would vary based on age because the daily life activities might vary based on age. But I'd also be interested in hearing some thoughts on whether the moral significance varies depending on the child's ability to either functionally consent, if not legally capable, for say, 14 and up versus assent, at whatever age you want to put assent, whether there's some variation in minimal risk based on the child's capability to assent. So, it'd be helpful just to hear some thoughts on that.

CHAIRMAN BOTKIN: Okay. We have about 15 and 20 minutes, so let me go ahead and read this last bullet, and then we'll pick up the conversation there. "Should the application of minimal risk be dependent on a child's and or developmental stage? For example, if an intervention is minimal risk for an adolescent, would the same intervention necessarily be considered minimal risk for a younger child? If not, why not? If yes, what's the justification for such an approach? For example, would such variation reflect the empirical differences

in risk exposure at different ages for the moral significance of child assent and or adolescent consent?" Steve?

DR. JOFFE: So, just to respond directly to Skip's question as I advocated a couple times over the course of the afternoon, the background activities of daily life of a one-year old versus a teenager do and should make a difference. But I think that the issue that you're raising, Skip, it's a relevant issue but we shouldn't confuse it with the question of what is or is not minimal risk. So, if a teenager can give a very advanced form of assent or can sort of ethically consent to participate in some activity, even though that may not be the same as legally effective consent, doesn't make that activity minimal risk. We may want to say, well, that older teenager should be able to agree to participate in this activity that goes beyond what the Subpart D regulations would allow and we may want to have yet another category if we could revise regulations to deal with this issue of ethically consenting older teenagers. But I don't think we should mix up the issue by suggesting that that somehow becomes minimal risk because the kid is now essentially consenting to some relatively riskier activity.

DR. KRUG: So, this is Steve Krug. My favorite example would be the driver's permit. That's actually something that the teenager assents to do. They actually have to fill out

the form. Different states have different rules and regulations and what not and that's also obviously something that fairly reasonable parents agree to. That's an enormously risk-filled activity and as best defined by your insurance premiums.

[laughter]

So, there's been some very careful data apparently done there and there're smart people who have figured out that your insurance should double or triple. To the question, I think that teenagers are uniquely equipped to both assent and or consent as we allow them to do for certain things and in doing so, we can raise the bar a little bit because first of all, it's not just a teenager. It's that responsible parent as well. So, I do think that the process and the perception or definition of risk can be developmental.

DR. BRADLEY: John Bradley. In terms of age, let me go down to the neonate, and it's a double-edged sword in terms of doing research. Traditionally, pharmaceutical industry has not wanted to do studies in the neonate because if there's any damage, it could be for the whole life of the neonate. So, we've been left with the neonates as therapeutic orphans, and half the drugs or so that are used on neonates, we have no good information on safety efficacy. And this has led to new FDA legislation just this past year that now mandates that every company who has any new product or new indication for a product

that neonates be specifically considered as research subjects. There's a neonatologist that's now required to be on all of these research study programs to ensure that neonates are included.

So, that is, in part, a response to the fact that no one wants to touch neonates but neonates still need medicines. But the downside of doing research on a neonate is that if you get it wrong and it's a toxic drug, you've not done a service to that infant. But at some point for these very sick infants with a whole set of congenital anomalies, there will be some adverse event. So, the risk-benefit ratio in studying neonates is a very difficult problem. We take more risks, but yet we need to study the safety and efficacy in neonates.

So, I would say that clearly we look at neonates completely differently than we look at any other age group. Their developmentally, their kidneys don't work well, their liver doesn't work well, their immune systems are poor, and they handle drugs completely differently. But there's a moral imperative to study them because if we don't then we're using drugs on them that may be dangerous.

CHAIRMAN BOTKIN: Okay. Quick comment from me and then a couple others. So, I'm wondering about this notion of sort of disentangling the consent piece from the risk piece and I agree with that sort of conceptually. But I mean, the reason

the risks increase in daily life for adolescents is because they've got more autonomy, because they're making more choices of their own, and we as a society think that's okay because you pretty much can't lock them in a room the way is typical for a one-year old.

So, is the reason that we would allow greater risk for research for an adolescent because we're comparing it to the daily risks of other adolescents or because we're giving them more discretion in their choices about risks that are relevant to their own health? So, I'm struggling to see whether we can sort of disentangle those two pieces. I think Loretta had a comment first.

DR. KOPELMAN: Loretta Kopelman. I think the primary thing is to think of it as an ethical decision, an ethical assessment about what is the minimal risk for your subjects. I can see that adolescents might find discussing concepts of death, for example, far less upsetting than younger children, or you might ask adolescents about their drug use or whether they're sexually active in questionnaires and those might be minimal risk studies where they wouldn't be for younger children. So, I mean, it seems to me obvious that you, in making the decision about what is minimal risk for your study subjects, take into account their age and their development. Am I missing something?

CHAIRMAN BOTKIN: Well, it sort of moves a little bit against the absolute standard of minimal risk if you're now saying, well, it's not actually absolute any longer, that it's much more acceptable to have a low risk for a young child and a greater risk for an adolescent because the background risks are different. That seems to me to move a little bit against some of the absolute standards that we've --

DR. KOPELMAN: I see the uniform standard as you're comparing the risk of the study to a uniform standard. That it's like you have a measure and you say, well, that is minimal risk given the children's age against this standard. For example, a pediatrician might well ask an adolescent about her drug use whereas they wouldn't ask a 6-year-old. So --

DR. GLANTZ: Yeah. This goes to the question of that it's not just risk, that it goes to the point that what is appropriate to do to one of these little subjects. So, as Norm pointed out that when you stick a 1-year-old with a needle, they think it's a horrible thing and when you stick a 14-year-old with a needle, they know that it hurts but it's not a horrible thing. Even when you look at the sense of time that little kids have versus older kids; if you say, how long will this take, 20 minutes is like forever for a little kid, right, and it's a blink of the eye for older kids and adults. So, I think their ability to withstand pain, to understand why the pain is being

inflicted has to do with -- I think there's an argument that we have to protect neonates and 1-year-olds and 2-year-olds differently than we need to protect 16-year-olds because they experience the world so much differently.

And I think that's a developmental thing. I should ask a pediatrician if that's a developmental thing. But how they experience pain, how they experience fear, how they experience anxiety, the issue of nightmares, things like that, I assume that that changes as a child develops.

CHAIRMAN BOTKIN: I have Norm, Ben, and then Steve.

DR. FOST: Well, just to add, again, data to Len's last comment, there was a study from the Yale Clinical Research Unit many years ago of kids that, as I'm remembering, they were roughly pre-adolescents, 10, 11, 12, and so on, who were admitted to a clinical research unit for non-therapeutic studies. Not particularly invasive. They were metabolic studies. Some of them were strapped into metabolic beds with urine and feces collection, and they had venipunctures, but nothing dangerous.

And then they were interviewed five months later and were asked about the experience and what it was. First of all, their ideas about what happened to them were astonishing. That is, they thought they had nightmares. They thought much more horrible things had happened to them. They were way more

terrified than their parents or their investigators were aware of and so on. So, it's a very different experience for a 9-year-old than for a 19-year-old. So, there is that difference.

I just wanted to take advantage of this bullet because I don't know that it comes up elsewhere, since we're in summary mode, to repeat my comment that I think the word "assent" should be changed "dissent." I mean, that's what it should be all about. It should be about whether the child says no, and no should mean no, and he or she shouldn't have to give any reasons any more than a 25-year-old who says, "No, I don't want to be in your goddamn study," shouldn't have to give any reasons; that's a sufficient reason. And that the 1-year-old is just as capable of saying no as the 21-year-old, and it's for very similar reasons. And that's why I think non-therapeutic venipunctures on 1-year-olds are very problematic, and I think we have to be more ingenious.

Last comment, my mentor Robert E. Cook, who made some of the most pivotal studies in the history of the world on the importance of potassium in bodily fluids that led to WHO electrolyte solution, saved billions of lives, did it by bringing infants from an orphanage into a research unit and heating them up and doing very careful balance studies. And in retrospect, he looks with horror at what he did and realizes that if there had been such a thing as an IRB, they wouldn't

have allowed him to do it, and he could've made the same studies on kids who were sick and who they could've done more careful balance studies without exposing them to stress. So, end of comment.

DR. WILFOND: Okay, let me try to think of what I want to say because I have potentially a lot of comments. Norm, I'm not sure I agree with you about the idea of dissent. I'm not sure I'm as confident of a 1-year-old dissenting or how to interpret 1-year-olds not being happy with something compared to a 5-year-old. I mean, I think there might be other reasons, as you're describing, for the studies you're describing why we might not do that in 1-year-olds but not because of the dissent issue.

That distracted me, I forgot why I raised my hand in the first place, so can I go onto Steve but maybe come back?

DR. JOFFE: Steve Joffe. So, I just have to press Norm and Len on this question of non-therapeutic venipunctures in young children. So, when my son was two months old, his pediatrician offered him to enroll in a study comparing two different vaccination schedules of the usual childhood vaccines. So far, no big deal. Essentially commensurate with vaccines that he would've gotten anyway. But the study required that he have two blood draws to check titers, 15 and 24 months, or something like that. I don't remember the details.

We said, sure, sounds reasonable, and we enrolled him and he got his vaccines, and he had his two venipunctures, and he cried and screamed when he had his two venipunctures, and that was the participation. So, I guess the question is, should the Boston Children's Hospital IRB not approve that study, and was I failing to be scrupulous parent in agreeing for him to be enrolled in that study that included these two non-therapeutic venipunctures?

DR. FOST: Yes to both. It's battery. I plan to call the police --

[laughter]

-- after this meeting and have you arrested and your house impounded.

CHAIRMAN BOTKIN: So, let me ask this simple --

DR. GLANTZ: So, I didn't say you shouldn't do it. What I said is that in evaluating it that the way we evaluate the nature of that risk should be different; that doing the venipuncture on your 1-year-old should be seen differently than doing a venipuncture on your 13-year-old so that it's one of the considerations that would go into it.

I'm not sure about assent or dissent, by the way, for a 1-year-old. I don't think a 1-year-old can assent or dissent; they are happy or unhappy. But the idea of 1-year-olds making choices; we make choices for 1-year-olds and we have to be

responsible for them. What's the nature of protection for 1-year-olds? And it may be that we don't have to protect from venipunctures but we shouldn't think that the reason why a venipuncture is okay in a 1-year-old is because it's okay in a 20-year-old.

CHAIRMAN BOTKIN: All right. We're leaning for the tape here, so let me ask this question. I don't know whether this brings anymore clarity to it, but let's imagine you're dealing with an adolescent population that has significant developmental disabilities, and they're at the developmental stage of 1- to 2-year-old kids. So, what would be the appropriate comparator for that adolescent population in terms of defining the acceptable risk level that you could pose in your research? And my assumption from the conversation is that it would be 1- to 2-year-olds; the daily life experience of 1- to 2-year-olds, as opposed to 15- or 16-year-olds, which don't really reflect the developmental stage of the subject population that you're dealing with.

So, does that sound right? And is it the fact that this research participant group, these adolescents, presumably can't give assent, the reason why we would want that lower developmental comparator, or are there other reasons that we think that's the right developmental level to use? Does that question make sense?

DR. GLANTZ: I think it's the right one because, and again, you'd have to tell me. It's sort of technical question. They experience the world as a 1 or 2-year-old would experience the world. When somebody in a white coat and a needle comes at them, if someone is 15-year-old but has the mental age of a 2-year-old, I assume they see it as a 2-year-old. Is that true? Is that what it means to be at that mental age so they'll be as scared, they'll be as frightened, and they'll be as unaware of why this is happening? So, we have an obligation to protect them differently than we would other 15-year-olds.

I think 15-year-olds can say no, right? They can dissent. I don't think someone with the mental age of 2-year-olds can say no so someone has to say no for them.

CHAIRMAN BOTKIN: So, it's really more than the permission piece per se. It's really how they experience the world and that --

DR. GLANTZ: To me. Yes.

CHAIRMAN BOTKIN: -- the more protected environment that would be part of their normal world and their lack of understanding, perhaps, of events and ability to justify or understand long-term consequences would be as relevant as their ability to assent itself to the experience.

DR. GLANTZ: Yeah. To me. I don't think the assent part matters; I think it's their understanding of it and our

obligation to offer more protection to that population than to the population of 15-year-olds who are now at that stage.

CHAIRMAN BOTKIN: Any other comments? Ben?

DR. WILFOND: Yes. My recollection's coming back a little bit. Well, I mean, I agree with the points that Norm and Len have made that younger children may experience things differently so that we could think of the risks differently. I think we have to be careful about playing too much into that, and I was actually struck by the example that Loretta gave about talking about death to an 8-year-old, you know. If this 8-year-old's dying, I would be troubled by the concern that this is suddenly more than minimal risk in them but not in 12-year-olds because this is what they're confronting and I think we have to be careful we can overstep it.

So, I just want to make that point that if we make these distinctions, we have to be very careful how we apply them and we don't preclude research that otherwise would be important because we made assumptions about the level of risk.

DR. KOPELMAN: Loretta Kopelman. Just to respond, we are talking about healthy; in minimal risk, we're generally talking about healthy people. I agree, talking to children about death who are very, very sick might actually be very liberating for them. So, I think that shows why we do need to

do a moral assessment of who your subjects are in terms of the study.

DR. WILFOND: But I thought we already decided that risk was based upon the average age, not based upon people who are --

DR. KOPELMAN: The measure. The measure is based but you're still making a moral judgment using the measure. So, it might be high risk to talk to -- I mean, I don't know which it is but I mean, I would assume it would be much more upsetting to some group of children than others to talk about death. But you're still using the same measure to determine minimal risk or trying to use the same measure in relation to your moral judgment about whether it is minimal risk for them. I still think it's a uniform standard.

CHAIRMAN BOTKIN: Okay. Excellent. Thanks everybody for a long day but a great day, and we are going re-meet at 8:15 tomorrow morning. And we're going to be talking about disorder or condition, and then allowable risk under 50.54. So, everybody have a good evening.

(Whereupon, at 5:34 p.m., the meeting was adjourned.)

A

Anthrax .5, 8, 9, 12, 13, 26, 30, 37, 51, 60, 63, 64, 65, 67, 68, 72, 75, 77, 78, 79, 81, 88, 89, 166, 168, 169, 183, 186, 190, 194, 201, 202, 203, 204, 221, 237, 241

Anthrax Vaccine ...45, 46, 90

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