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TRANSCRIPT

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(15-minute break) --

DR. GUTMANN: Welcome back, everybody. We are turning to the regulatory mechanisms for distributing and studying Medical Counter Measures in an emergency and several Commission members suggested, as did many people who presented to us previously, how important it is that there be preparedness and we'll begin with a brief presentation from the Commission's Executive Director, who is also an expert bioethicist in her own right, Dr. Lisa M. Lee, who will review for us what are the regulatory mechanisms that exist for distributing and studying Medical Counter Measures in an emergency. Dr. Lee, take it away for us.

DR. LEE: Thank you. A couple important things as we discuss how we'll go about distributing and studying Medical Counter Measures in the event of an event include that distribution for treatment and distribution for research are different things, as we've discussed. In the case of an event, we'll likely be most concerned, obviously, with treatment and making sure that we've managed the event, but we also will have an opportunity, as we have been discussing this morning and other times, to do some research that otherwise we would not be able to do and some will be observational, obviously. And there are certain mechanisms the FDA has authorized for us to do, to enable, unapproved products to be studied and used for treatment in an emergency. So the couple of regulatory mechanisms we've talked about these briefly with some other folks who talked to the Commission before; those two things for off-label use of approved medical products or things that are virtually unapproved at this point. These two mechanisms being Emergency Use Authorization, or EUAs and Investigational New Drug applications or I'll call those INDs.

These two tools allow for promising but unapproved pharmaceuticals to be used in an emergency. The first one I'll talk about are the EUAs or Emergency Use Authorizations. The key with this one, as I mention, are the promising but unapproved pharmaceuticals. One piece of the definition and the other is public health emergency.

Two things need to be defined here. What is a promising but unapproved pharmaceutical? There has to be some scientific evidence that indicates the product might be effective against either a serious or life-threatening agent. So some data have to be available, this can't be a brand-new biologic or brand-new drug. There has to be some known or potential benefits that are outweighing the known or potential risks and ultimately no other alternative, it has to be our only option.

In terms of definition of public health emergency, this has to be something that has been declared by the Secretary of Health and Human Services, and it involves an agent or pathogen that has potential to cause serious or life-threatening conditions. The situation would be dire if we were in a situation to use one of these tools.

Now, in terms of use during a public health emergency, the EUA allows us to use a product, not to study a product, but to use a product. So, this is not a research tool. It does involve some pre-planning and, actually, in order to use it, we have to know what we'd be doing in the case of events. So the FDA allows for what they call pre-EUA planning, most EUAs are in the pre-EUA stage, because we are not most of the time in an event, so most of the EUA's that exist are in preplanning. This happens where an authorization has happened far before emergency is declared. The FDA can take time to review the situation and plan before an event.

The clinical use then is subject of this agent is -- I'm sorry, drug or biologic, is subject to strict limits. It does use a clinical consent paradigm, however, there is not an IRB review, there is not research protocol as I mentioned. The goal is to really give timely access to a product during an emergency. As I mentioned, it's not a research tool, so there are not research protections under Emergency Use Authorization, the use is the key word there. And limited data collection is allowed. There is the provision for some basic data collection, so we can observe what is happening during this limited use, but it is not at all near the research perspective.

Also, so if we think about the use specifically to the Anthrax situation, an EUA would be something we could use in an adult, because we do have some information, some data on safety for and efficacy for adults. So an FDA pre-EUA for use of AVA as a post exposure prophylaxis in adult does exist, and those data we have for adults come from the pre-exposure AVA use we have for many families and first responders, as well as military. So we do have data. Those data support the EUA for adults. For children, as we've talked about, no data exists for AVA. So we can't use an EUA for AVA for children.

What do we do for kids in the case of an event? We turn to the Investigational New Drug application, the IND, the other tool. That tool, the IND, allows for commencement of clinical testing for an unapproved drug or biologic product. No testing done, we have no information, this IND allows for us to begin that. Tough to begin that in the situation where we're in a stressful or potentially chaotic situation in an emergency.

But there are three kinds of INDs. One is an investigator IND, and this is in your normal situation, just interested in a product, want to investigate its usefulness clinically. A researcher would initiate and conduct an investigation of a new drug, or a vaccine. A treatment IND is an IND that allows for the use of a promising drug or biologic for treatment with patients that are not in the trials that an investigator is doing. And then, finally, there's the emergency use IND and this is a tool that allows for individual patients in extenuating circumstances to get a hold of investigational drug. We are not going to talk a lot about that, but we will talk about the emergency use of a treatment IND. So just so we clarify around the language, we're talking about the emergency use of a treatment IND.

In a public health emergency, the requirements for the emergency use of a treatment IND, which we would have to do in terms of a drug with no data associated with it yet. It would be a required drug intended to treat serious or life-threatening condition, the drug would need to be under investigation or in trials that are completed. So, a treatment IND is usually paired with an investigator IND. They are often called a nested treatment IND. So, an investigator would have a trial that they would be doing for a new drug, and then the treatment IND would allow the drug to be used more broadly, not just for the people in the clinical trial, but also other places. So, the sponsor is actively, would be actively, that means the person doing the trial, would be actively pursuing approval of this drug or biologic, and then the potential benefits again outweigh the risks, just like in an EUA. And again, no satisfactory alternatives available. Again, both of these tools for a situation where we don't have any other options.

Specifically for a public health emergency with Anthrax, again, with children, in the absence of any pediatric data, an IND is a feasible mechanism for delivering AVA to exposed children. Coupled with this investigator IND, data could be collected to inform future use for potentially using an EUA if we needed to use AVA in a future situation. An IND in this

situation would be under a research protection paradigm, unlike the EUA for adults, which is a clinical paradigm, this would be research protection paradigm. Things like an IRB review using written parental permission and meaningful child assent.

So, to summarize in terms of the mechanisms and how they would be used in terms of an emergency, we would have for adults, because data already exists for pre-exposure prophylaxis, we could use the EUA in post-exposure prophylaxis for adults under this clinical consent paradigm, and for children, the investigator and treatment IND under the research protection paradigm.

So, just to summarize then, we have these two tools, one useful for adults for the use, also allows us to collect a small amount of data and the treatment investigator and treatment IND coupled to allow us to use AVA for children during an attack. I'll take questions if anyone has any clarifying.

DR. GUTMANN: Yeah, and we'll take any questions on clarifying this, and then I will summarize, and we'll get into how we are proposing, as a Commission, to use these mechanisms post-event. Lonnie.

MRS. ALI: Thank you Lisa. Help me understand, is AVA considered in children, it would fall under the research protection paradigm, correct?

DR. LEE: If used under an IND.

MRS. ALI: An IND would be used in an emergency situation?

DR. LEE: For children, yes.

MRS. ALI: That would mean that an IRB would have to be convened and review the protocol prior to AVA being given to children?

DR. LEE: The FDA has some latitude in the emergency use, they can do-- there is also just like with the EUA, there is a pre-IND time where the FDA can review the protocol, can work with an IRB to do some review of that prior to an event. The piece that logistically, I think what you are getting at, are what are the logistics for getting this all done and quickly? Because in the situation of an attack, antibiotics would need to be delivered within 48 hours or so, the AVA actually would need to be delivered within days- 10 or 14 days. In terms of the lag for an IRB, that would be a big problem. So the FDA has discretion and-- both in terms of pre-approval, pre-IND, and also in terms of potentially waiving that or making an exception for IRB for a particular situation.

MRS. ALI: I say that couched with the comment made by Christine that the government does plan to give children AVA drugs if--

DR. LEE: Yes, yes, uh-huh.

DR. GUTMANN: Christine.

DR. GRADY: Maybe I can ask a question about that. My understanding was that a pre-review and approval of a treatment IND for AVA in children was already in place?

DR. LEE: It exists at CDC, they are the holders of that-- pre-IND has been -- CDC is the holder of that, yes.

DR. GUTMANN: Nelson.

DR. MICHAEL: Yes, essentially that is what I was driving at, reading the 2009 CDC guidelines says the use of AVA in children is not contraindicated in the post-event setting opposes a high risk for exposure, aerosolized B. anthracis spores, during such an event, public health authorities will determine whether, the under existing IND protocol, to vaccinate children, ages 0-17, under this IND protocol, three doses of vaccine, et cetera.

DR. LEE: Correct. Uh-huh.

DR. MICHAEL: So, I guess, in your view, this would be extension of that existing IND?

DR. LEE: Correct.

DR. MICHAEL: That could be done relatively efficiently.

DR. LEE: Yes. Correct.

DR. MICHAEL: So, I think that is important to clarify-- this clarifies and substantiates some of the discussion we had earlier about the fact that, when it's distilled to practice post-event, you're very likely to see children offered both vaccine and drugs.

DR. LEE: Yes, in fact, ACIP recommend that be done on a case-by-case basis, but HHS has said they will make vaccine available to children, as well as to adults.

DR. GUTMANN: Dan.

DR. SULMASY: Another clarification about the logistics. If I understood you correctly, the children's parents would need to sign an IRB-approved consent form for each child who will get this?

DR. LEE: Correct.

DR. SULMASY: It is just another issue out there in the field.

DR. LEE: And it is an excellent point in terms of the concerns of the folks in public health response, there are concerns about parents, adults, getting this through an EUA, which is a clinical consent and just yes, please give me the vaccine. And their children, who might not be present with them at the time of an attack, needing to have a written consent, parental consent, to have their child immunized. So, the logistics are not a breeze.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: Quick clarification question. So, I am -- let's assume that I'm, you know, internist with a specialty in ID, and especially interested in AVA. I want to conduct physician initiated IND to study the immunogenicity of AVA and I would apply to FDA, I would be denied?

DR. LEE: Well, I'm not FDA, so, I'm not going to make that--

DR. KUCHERLAPATI: Ok. But according-- based on the rules you just talked about. You talked about post-event, but I'm talking about today.

DR. LEE: Pre-event. Part of our question, you mean for children?

DR. KUCHERLAPATI: For children.

DR. LEE: Part of the question facing you all, the Commission, is should these types of studies be allowed to go forward? We don't have a protocol, we are not even at the point to have a protocol. You know, we're going to answer, help answer the question to the Secretary what are the ethical considerations that need to be, you know, out there, before a protocol could even be given -- to even consider it at the FDA, HHS or governmental funding for such a thing.

DR. GUTMANN: Other questions for Lisa? Lisa, stay up here for this.

DR. LEE: Ok, sure, absolutely.

DR. GUTMANN: You were right the first time you said our deliberations. You've been extraordinarily helpful, instrumental, and extremely knowledgeable in helping us move our own deliberations forward. So, let me just summarize, as Lisa explained, and then move it a step further to where we are in our deliberations, and open it up and I'll ask Anita to say more. I'm going to do a very high level summary.

So the FDA currently interprets the provisions of the EUA, the Emergency Use Authorization mechanism to require at least some data from pediatric testing before an EUA can be issued for pediatric Medical Counter Measure use in an emergency. It is preferable, we think, to use the EUA mechanism when data are available to characterize the intervention in pediatric populations. Because children react to drugs and vaccine differently from adults, the heightened safeguards of pediatric research protection are appropriate for an intervention that is completely uncharacterized in children. It also, and therefore, makes sense to us to endorse the FDAs approach to the use of INDs or Investigational New Drugs. That is, when there are no existing data on the administration of a Medical Counter Measure to children, and it will be made available to children in an emergency. It should be provided under a treatment IND, that's to ensure that rigorous pediatric research protections apply and, at the same time, we're saying there are, and should be, advance preparations to expedite this. Such protections include, for example, independent review by a local IRB, in the case of an emergency expedited review, when a Medical Counter Measure is distributed broadly to children using a treatment IND, it is also essential to conduct a concurrent small scale study under an investigator IND to obtain data that could potentially be used to support an EUA for pediatric use of the Medical Counter Measure in a future event. So, planning for post-event research is also essential and to expedite post-event research and ensure the availability of appropriate Medical Counter Measures for children, a pre-IND consultation and approval should be put in place before an event. And that is-- I think a good summary of where we, as a commission, propose, you know, what we think we stand now with regard to recommending preparation, full preparation in the case of an emergency.

And I'm going to ask Anita to take it from there, because Anita has been very involved with other members of the Commission have in these deliberations.

DR. ALLEN: Thank you, Amy. As you said this morning, we all hope that the events never unfold that would give rise to the need to play out the post-event pediatric Medical Counter Measure scenario that we're responding to, that we're poised to make recommendations about. But we have to be realistic, we can't hope that our government turn a blind eye. As a country, we have to be prepared. This morning, both Nelson and Lonnie emphasize that we need to be ready to carefully deploy the appropriate and ethical Medical Counter Measure to everybody who stands to benefit, including children.

So, as I understand where our deliberations have led us, we are poised to recommend a set of carefully devised post-event emergency responses that kick in when children have been exposed to relevant biohazards, and also when there is an imminent threat that they might be exposed. I think about it in terms of there being a substantial likelihood that exposure will take place, that is using my tort law discourse there, substantially certain to occur.

So in our aim is to always be, in our recommendations, sensitive to demands of beneficence and respect for persons, parental and individual autonomy, allocational justice and deliberative democracy through both accountability and also public engagement. So here is what I think we're briefly prepared to endorse. First of all, I think we're prepared to endorse swift delivery of therapeutic Medical Counter Measures to exposed and imminently exposed children, whether they have been tested earlier or whether or not they have been pre-tested and children pre-event, we think it could be ethically appropriate to deliver countermeasures. But we also believe that there must be promptly initiated both data collection, observational, investigational type research aimed at better understanding such concerns as safety, immunogenicity, efficacy and dosing to the extent consistent with the child's health and recovery. We do think that children may benefit directly from such research, which renders it ethical in a way that would not be ethical prior to the event. We also seem to agree that post-event research should be constrained by existing regulations having to do with limiting research to minimal risk or minor increase over minimal risk in children who won't directly benefit from the research. So, I'm just going to state a little bit more about both of these categories, the testing and the delivery of the countermeasures.

First, as to research. I think what we're saying is that research is ethically required post-event, not just okay. We are recommending that there be follow-up research to determine the effects of delivering a Medical Counter Measure that has not been previously tested on children. How does it work? How safe is it? How effective is it? We want to look at those kinds of questions to the extent we can. It's going to be both prudent and ethically necessary to take stock after the deployment of countermeasures, and one issue that I think our group might want to discuss a little bit more today is whether passive surveillance based on self-reporting resources is all that is necessary in the event of delivering a countermeasure that has not been tested before on children. Do all we do is just wait and see what happens and based on self-reports, or should there be some research protocol that are developed to more systematically gauge the effect of the countermeasure?

I think we're also recommending, again, research, both surveillance type and investigational research post-event, and that if the decision is made to treat children with a drug that's not been tested, we should be mindful of what kinds of protocol would be ethically required and permitted in this context. There are choices to be made about whether nested or independent type investigational clinical trial research is best from a scientific point of view and

I leave my scientific colleagues to comment on that. Do we want to have the kind of IND nested research happen or have other research happening on the side in addition to that?

To best protect children in accord with traditional ethical constraints, we're endorsing deployment of untested Medical Counter Measures, but within a framework of a non-research FDA IND. Lisa just nicely described a kind of paradigm of investigation and treatment IND which is very protective. This kind of research would be, except in a very, very emergency emergency situation taken by IRB approval, there would be assent and consent involved, there would be preplanning consults with preapproval, hopefully, for this type of research and these kind of protections, the pre-consult, the IRB, the consent, the assent, would mean this kind of research would meet that ethical demands that we think are important in this context. More so than the Emergency Use Authority which not only would not be appropriate because the drug has not been tested in children, but also don't come with any kind of research based add-ons and the IRB approval.

So, okay, so, applying our recommendations to a framework, to the Anthrax vaccine, we're assuming that post-event children would be given the vaccine and antibiotics, even if the vaccine had not been yet tested, or thoroughly tested, and our approach, I believe endorses such a possibility, but recommends that there be ethical monitoring in the form of ethically designed follow-up studies for data collection and also any other investigation or treatment IND-based research that could be done within the prescribed paradigm. So, all of this said, I am left wondering about some of the concerns raised earlier about how quickly can we deploy all of this? Less than a month? Less than a week? Will there be political pressure to put aside the protection that we ethically recommended? I hope not. I do think we need to talk about the what kind, specific kinds of research we are thinking might be done that would be beneficial in the context of an investigation and treatment IND and ensure that we think those research, the ones that scientists would say would be useful, would also be ethical, but it seems to me that with IRB approval, this framework of the investigational treatment and IND paradigm would work quite well and would be ethically sound. And I hope we never get to the point of trying to set aside ethical guidelines in order to respond to an emergency in a somewhat rash manner. So I will stop there.

DR. GUTMANN: Thank you, Anita. That was a really excellent summary of post-event process and substance to meet ethical principles that would satisfy those in a post-event setting. We say that it has not been tested in children and that is correct. We, also, just to remind ourselves and anyone listening, we also recommend or we are poised to recommend that there be age de-escalation testing consistent with minimal risk research with children, and that could start any time and get, at least for older children, some possible data. But everybody who has spoken to us agrees that there would be the need, and we agree with this, there would be the need, still the need for research testing under ethical standards in the case of an event. With that, I'll open it up for any discussion, questions, comments. Dan, why don't you begin?

DR. SULMASY: Yeah, one thing that sort of concerns me as we move to talk more about post-event testing is that I'm not sure our deliberations so far have given sufficient attention to the sort of general literature on the ethics of disaster medicine. I think we're sort of thinking of this as sort of our nice research protocol and all of the sort of clean ethics we'd like to see with it, but I've said before, I was at St. Vincent's Hospital when several hundred very self-important NBC employees descended on the emergency room within hours of a cutaneous

exposure. I think that's nothing in comparison to the kind of widespread panic and logistical difficulties that will ensue in the event of the kind of disaster we're thinking about, you know, questions of potential for overwhelming resources, even clinically to distribute the drugs, the panic, etcetera, need for triage possibly if we have shortages, and I think we have to be thinking about that as we are framing any kind of research protocol. Certainly we can talk about preparedness, talk about preparedness from a public health perspective, and about research logistics. But, I also think that we ought to be careful to think about, as clear and simple research protocols as we could imagine if there is going to be anything in this kind of a setting, because the simple fact is the kinds of things we tend to think about in the clinical research arena are not going to actually be feasible in this kind of realistic setting, and I just think that we've got to be more attentive to those kind of concerns than I've heard in our deliberations.

DR. GUTMANN: Nelson?

DR. MICHAEL: Just to answer or to offer one answer to question that Anita posed to us, which is the question of a passive survey versus a more active surveillance of those vaccinated. I would come down pretty definitively on the latter. I think that this would be a situation where you are going to be taking the risk of going off a bit into the scientific unknown to vaccinate children. I think that it would be ethically important for us to do the best that we could to ensure that there is ongoing observation of safety in those circumstances. Because, we may learn something that might cause a national change to practice in the case of doing those kind of studies. So, I would feel very strongly about in a post-event situation to do active monitoring and not a passive reporting system in a subset of individuals.

DR. GUTMANN: Steve.

DR. HAUSER: Yes, I was going to make a very similar point. I agree with that. We all know that the awareness of potential adverse events can create false alarms that are very common. And one question that I have with respect to an active system and where a treatment IND and an investigator IND opportunity may, where that limit is, is an active surveillance event is not a small nested study, but suggests a larger study that potentially might also include people who opt out, but are in the high-risk zone as a control population. And how do we think about those very practical issues that would be involved in an active surveillance concept.

DR. GUTMANN: Lisa, do you want to take a stab at these really important questions for us to consider?

DR. LEE: Sure. I think that the issue around studying that in an active monitoring kind of way for people under the treatment IND, and remember that the treatment IND is for people not involved in the trials of the drug. So, remember, we don't know much about the drug to start with. The people under the investigational IND are people who are in the clinical trials. Does this drug do what it is supposed to do? What's the right dose?, etc. All of the phase 1-3 clinical trials. Those under the treatment IND are people who aren't in those clinical trials, but who in the case of an emergent event could benefit if there is no other option. Included in that treatment IND could be something around, as we're discussing, these active monitorings. And if the active monitoring would need some comparison group, that could be something, I'm sure, that could be built in, whether it is, probably wouldn't be people under a treatment IND, but we could do lots of vaccine research for adverse events, look at an appropriate comparison group, so. But I think

there is absolutely a way to look at that and lots of vaccine researchers that do this kind of work that could design a study that could get to that.

DR. GUTMANN: Christine.

DR. GUTMANN: Raju.

DR. KUCHERLAPATI: I want to follow-up on Dan and Steve's comments and ask a very pointed question. Anita said that the population that has been exposed, that it's ethically imperative that they should be studied, I think that's good. And also, the point that is made is that the kinds of studies should be not just passive studies, but active studies to really understand that. And the question that I have is that those active studies might include the kinds of interventions that would be currently be considered to be greater than minimal risk or significantly greater than minimal risks. And we have, so we have said that under no circumstance will children be exposed to any type of research studies that would involve greater than minimal risk, so the definitions of that have to be clear that what are the kinds of things that might be permissible under those circumstances that might not be included in the current set of guidelines for what is acceptable and not acceptable.

DR. GUTMANN: Do you want to respond?

DR. LEE: In the case of post-event situation, there is possibility of benefit, direct benefit, the idea of greater than minimal risk changes, so what we were talking about in terms of limiting or capping at a minor increase over minimal risk is for the pre-event situation where there is no off-setting direct benefit. We're talking now about a post-event situation, where, if we get in a situation where there might be something as you said, it is not necessarily that the actual, let's say in this case, it's a vaccine, the vaccine might not be greater than minimal risk, but the other observational things, if you have to do many blood draws or do some other research related intervention that would be considered greater than minimal risk, that could happen and that is parsing out the risk. The research risk is greater than minimal, that could be allowable. We'd have to see the -- we're not the people deliberating the protocol, an IRB would have to look at that. In the case where there is the possibility of direct benefit or the idea that there is -- that the child themselves would benefit. Now, whether that study would be designed in an event of a bioterror attack remains to be seen, but there is that possibility. When there is direct benefit to be had.

DR. KUCHERLAPATI: Can I just-- I understand that, but the question for us is whether that should be articulated in our report.

DR. GUTMANN: Yes. Our plan at the moment is to articulate that. If the situation changes, there are still ethical guidelines, but they have a different implication when children stand to directly benefit from research. And then you want to impose no more than necessary risk. The risk has to be proportionate to the benefit, and you still want the consent, informed consent of parents and, assent, if possible, of children, but there is a direct benefit to the child, and that is-- makes all the difference, and we absolutely will make sure we articulate that in the report. I see Anita.

DR. ALLEN: I just want to clarify, would this be accurate to say simply that post-event research should still ethically be constrained by the existing regs 405, 406, 407. it's just that they

would have different implications in the context of what is direct benefit and the risk is proportionate, so we are still within the same framework, but now we might be allowed to do some things we wouldn't have been allowed to do pre-event, right?

DR. GUTMANN: Absolutely correct. The ethical principles are constant, their implications change for when a research subject who is a child stands to benefit versus when a research subject who is a child does not stand to benefit. They also change with adults. But, the very big difference, extraordinarily big difference, between adults and children is children can't themselves give their informed consent, so it is incumbent on us to add protections to prevent exploitation and other any other injustices to the child. Jim.

DR. WAGNER: Just a very quick point. I know that is a little side of what you just said, Anita, under the circumstances as we talked in the past, we would imagine more risk. I would hope that when we document this in the report we wouldn't talk about being allowed to take more risk, but reluctantly having to accept more risk by pursuing these kinds of protocols.

DR. GUTMANN: Nita.

DR. FARAHANY: I have just a couple of maybe definitional questions, given the conversation we're having. The first one is the stand to benefit language, so-- especially with the conversation we're having earlier about exactly how you would define post-event and who is included within post-event, is the idea stand to benefit now any child who might potentially be exposed to Anthrax, and if we were imagining a scenario which Raju had outlined which is there is event in Boston, but we think about it as being potentially imminent across the country. Does that mean that the stand to benefit applies broadly such that the types of risk you could expose a child to post-that event would apply to everyone, and then related is we're talking about consent, I know we are going to and have talked a bit about the framework for consent and how that is different and the post-event framework. But how do we safeguard that in the post-event framework where there is fear because an attack has already occurred, the likelihood of being able to obtain a more objective type of consent is diminished because of the concern, so the reasonable parent standard may change under the circumstances of an event having already occurred?

DR. GUTMANN: Do you want -- do you want to do both? I would turn to you for the second part of it, feel free to do the first part, if you want. I'll take the first. It's important that imminent not become potentially imminent, as you put it. Imminent is imminent, and if it's not imminent – but-- we live in a potentially imminent world, where many things are potentially imminent, so potentially imminent isn't enough. It has to be imminent, and similarly with “might benefit”. That is just too vague, we have to keep the standards that there is in the case of, we are talking about post-event, there needs to be knowledge that if children would be subject to more than minimal risk research, they would stand to directly benefit from it. And there are procedural ways of testing that, so, as Lisa said earlier, if we are in an emergency situation or imminent emergency situation the Secretary of HHS would say so.

It can't be just somehow whispered in the ear and kept confidential and then all rules or at least the normal rules are lifted. I think we need to be, you know, just clear about that. And then I turn to you for the second part.

DR. LEE: Thanks. Just one quick comment on the potentially beneficial first part. There is -- there has been some work done to define direct benefit and indirect benefit and another even further out, or more distal benefit, the aspirational benefit. We can look at that, and think about, there are some good working definitions of direct benefit, and I think we can come to a place where we agree on what that means. So, I do think that that is important for us to think about, consider and define clearly, because we can potentially benefiting could be anyone, as you described. So, the second part, remind me again, what the --

DR. FARAHANY: The informed consent issue with, you know, especially the reason for them to gather, right, which is, if it is a direct benefit, the likelihood of consent.

DR. LEE: Right. So in the situation of an event, you know, when we're thinking about ,again, we have to separate the fact that we're going to be treating and then doing research so the treatment consent, we would use an IND here to treat kids with and that -- there is a parent who is thinking about treating the exposure. In terms of the risk and the motivation for the parent to consent, it's clear they want treatment for their child. The risks seem high, they want treatment. In terms of agreeing to do research, that is a different set of considerations for parents. So we would, whether the motivation is higher or lower during an event, for the research piece, you know one could imagine two really different sets of motivation, either all I need is to take care of my child and I don't have time to think about anything else, or this is a situation where we have one opportunity to do something really amazing and I'm going to take it, but in terms of coercion or highly motivating parents because of a sense of the stressful situation around the research, less of an issue than around the treatment.

DR. FARAHANY: Let me just follow-up on the treatment part because that is part of what I'm thinking which is presumably the treatment IND would be approved, not just for people who had certainly been exposed, but potentially could have been exposed or within a zone that could be exposed. So, the line between treatment and research becomes a bit blurred there, where you have a number of people who are simply within the direct benefit, you know, purview, but who may not in fact have been exposed. And so, I'm just worried about the people who would consent and how you obtain meaningful consent under those circumstances where we can't know for sure, or the idea that the treatment IND only applies if they're, its proven exposure for that individual. I assume not.

DR. LEE: No, but I do think it is important to keep, so your point is who wants to get the vaccine under the IND, the treatment IND? And the treatment IND is exactly for that: for treatment, so if a parent says I want this treatment for my child, whether you, healthcare professional, think they need it or not. That's not a research related risk or consent issue, that is a treatment related consent issue. A parent could still say, I don't care, it doesn't matter if my child was exposed or not, I want them to participate in the research. And face whatever risks I'm willing to allow them to face. But for the treatment piece, it's like a parent going to the pediatrician and insisting on antibiotics when they have a viral infection, the same, I want this no matter what. The treatment doesn't really have to do with whether they've accepted risk or not, it's treatment separate from whether they want to enroll in a research project that is going to benefit someone other than their child. So the risks one takes on for treatment is risk for themselves often because there are lots of benefit to be had. The risk one takes on in research is risk for others, often because there aren't benefits for oneself.

Dr. GUTMANN: Dan?

DR. SULMASY: Yeah, I just wanted to also caution us to be careful not to go too far in the direction with our language about direct benefit of assuring that we know that there is going to be benefit. Otherwise we're, you know, engaging, there is no reason to do the research and we're slipping over into the therapeutic misconception, so we want to say I – I think we do want to say that there is a reasonable prospect of direct benefit.

Dr. Lee: Sure. Great point and I think that language is really important. We must say prospect, because if we knew, we wouldn't need to do research. Well taken, thanks.

DR. GUTMANN: Christine.

DR. GRADY: I think it is true in the post-event setting the treatment IND and the research IND would be coupled in a way that some of the same kids would be invited to participate in both.

DR. GUTMANN: True.

DR. GRADY: So, the consent process is going to be very complicated because in that setting, one would have to be able to explain to a parent the difference between receiving the offered MCM and participating in research. But, I think it is also true that a treatment IND requires written consent in every case, right?

DR. LEE: That is true, and it's much more like the research paradigm, consent paradigm than it is the -- true, for the treatment.

DR. GRADY: Yes.

DR. LEE: Right.

DR. GRADY: So it is going to be a complicated, practically speaking, situation.

DR. LEE: Extremely.

DR. GRADY: One question for Raju, actually. I'm having trouble imagining what you have in mind about procedures that are greater than minimal risk in the setting, in the post-event setting? Do you think like liver biopsy, what would be done that might be greater than minimal risk? Because, I mean, the language in the regulation is pretty specific that it is the procedures or the interventions that we're talking about in terms of measuring risk and benefit. It is so interesting to think about in the post-event setting, if everybody is offered the intervention under treatment IND then what research procedure might fall into -- imaginably fall into a category of greater than minimal risk?

DR. KUCHERLAPATI: For example, lumbar puncture. We talked about that, under normal circumstances, that would not be considered to be, you know, routine procedure and that may be required. Right? Or, in other cases that I think about, if there is infectious agent that infects the lung, maybe plural fusion would be a procedure. Liver biopsy, any of those types of things, it is not possible for us to be able to determine exactly what the nature of those things would be, but certainly there would be variety of different types of procedures or information

that you might want to obtain that will absolutely be prohibited under the current set of guidelines for research involving children.

Since I have the microphone, can I make another comment? At least I wanted to follow-up and make sure we understand this clearly. Under normal circumstances, an IND, an Investigational New Drug, if I'm applying for it, if they have a regular procedure, first of all, you have to do Phase I trials to be able to assess the safety and then Phase II escalation trials address toxicity and Phase III trials that would really involve efficacy. In this particular case, we will not be going through all of those different sorts of phases, it is just a mechanism by which the drug at a given dose that would be predetermined would be given basically to patients. All right?

So this IND that we're talking about is completely different than the IND that normally would be utilized and so the kinds of regulations that govern them are completely different.

DR. LEE: That was a question. Yes, that is correct. Now there is the option to do, so that would be the nested, that is why they call this nested. You have an investigator IND that's going through that. Inside that, you can do the treatment IND that allows access, in an emergency situation to do this treatment based on, as you said, a pre-set, in this case, likely give children the adult dose because we don't have any other best guess.

So, there is an option to do kind of a parallel treatment IND, in which we would make a best guess, a different guess, maybe not a best guess, a different guess for dosing for kids. Well, maybe they should have half the dose but, it's extremely difficult to justify ethically messing around with dose and not knowing what dose to give in the middle of an attack. Who is going to do that or think that is a good idea? Right. It is possible, it's just not ethically the right thing to do.

DR. GUTMANN: Let's keep in mind that a lot, I know we are focusing on the immediate aftermath, which will be stressful if there is enough preparation, not chaotic, but very stressful. But remember that a lot of the research findings that are needed here are over a long period of time, so we shouldn't, while it is true that the most challenging part will be how one begins, most of the research will be over a significant period of time, and as long as the government is able to provide the vaccine and antibiotics in a timely fashion, as the stress gets lower and we overcome the initial reaction, there's going to be a lot of need and time for ongoing research, and I think part of our job is to also make sure we don't lose sight of that given that, given that we have the time to deliberate and I saw Christine, and then I have an important question from a member of the audience.

DR. GRADY: I just wanted to comment on Raju's question. I think, I think, although I could stand to be corrected, that is where Anthrax differs from some, potentially other, MCMs. And I think the reason that we can think about a treatment IND for Anthrax vaccine is because there are so many data already in existence for adults. And so, the phase I, II, III that you talked about, that's already occurred for AVA in adults. And so we can do a treatment IND. In another case, where we didn't have so much data, it might not be possible to do a treatment IND, I think.

DR. GUTMANN: Mary Coombs, Miami School of Law.

Mary, where are you? Welcome and thank you for this question. Mary, as you point out, pre-event MCM may, and we hope, produce research results that will never be used. However, it

is clear that if an event happens, and we're less prepared than we could have been, there is likely to be severe loss of confidence by the public and the government's ability and willingness to protect the public, which has significant public health risks. Can this risk be considered at the margins ethically? Perhaps and this is, I think, the question and suggestion actually. Perhaps, so we don't narrow minimal risk, because an event may never happen, so basically this is a recommendation to us not to overly narrow the understanding of minimal risk.

Who would like to -- somebody should respond on behalf of the Commission or at least on your own behalf. Yes.

DR. KUCHERLAPATI: I agree with that view and I think that is some of the view that some of the Commissioners expressed today that the fact that we may not know whether this event is going to happen or not going to happen should not diminish the importance of obtaining as much information as we can obtain prior to the event, that would really help us. So I am completely in agreement with this.

DR. GUTMANN: I think that our recommendation, which we have discussed earlier and we haven't yet issued it, but we've discussed it, which could begin as we speak if the government wanted to do, is do age de-escalation, beginning by looking at what the data are and, if necessary, do more research on young adults and begin with age de-escalation on the oldest children, if you will. So, if you looked at 18 to 24-year-olds or 19-24-year-olds and then inferred minimal risk 16 to 18 year olds-- again, there are data there for adults, but they haven't been yet analyzed in a way that would suggest the possibility of proposing a protocol bringing it before an IRB and doing what can be done at minimal risk right now. And that is something that we have discussed earlier and, as of now, I think we're prepared to recommend that. Dan.

DR. SULMASY: Just a point of clarification about that. Some of our discussions have led me to believe we might be recommending that even if we're determined to be minimal risk research, we should do age de-escalation within that and I think that if that were the case, that would be too restrictive. What I think we need to be clear about, which I think what we're saying, is that by doing age de-escalation protocols, we turn what would be by definition, because of the uncertainty, more than minimal risk research, into minimal risk. And I think that we have got to on be very clear about that.

DR. GUTMANN: That is absolutely right, I mean, we have been focusing, because we've done so much focus on pre-event, on post-event, what Dan said is absolutely right. The reason for age de-escalation is because, as of now, we cannot have confidence and we've been told -- we have not confidence there could be minimal risk research on all age groups. Indeed, we have been told that is not the case. And therefore it would take an age de-escalation set of research procedures to do that. You made a narrower point, this is -- which is, don't make minimal risk research -- don't define minimal in an unrealistically narrow way, or overly narrow way, which is a point well taken. The larger point that we have to do is we have to give examples of what minimal risk research is, and we have to avoid the Scylla of over narrowly, making it too narrow, and the Charybdis of expanding it so it is no longer a meaningful protection for children. It must be a meaningful protection, particularly in the case of children who do not directly benefit from the research. I have Christine and Nita.

DR. GRADY: This is an issue that I think we need to discuss a little further because, I have trouble with the concept of being able to make something minimal risk research. I think more research gives us more data, allows us to identify the risks, allow us to categorize them and allows us to determine whether they are acceptable in some way. But it doesn't necessarily make them minimal if they are not minimal. And so, somehow we have to be careful about the wording we use in terms of what we're trying to do in terms of more data.

DR. GUTMANN: Fair, fair point--

DR WAGNER: We can discuss--

DR. GUTMANN: --we weren't making it, we were determining whether there can be minimal risk research, that's important. Right?

DR. GRADY: One more point, I think, perhaps, I don't know if we fully discussed this, but perhaps if there is a very careful and method of determining what the risks are in older children and, first, young adults, and older children working down, it might even be true that the risks are acceptable even if they are not minimal.

And that's something we haven't really discussed.

DR. FARAHANY: I just wanted to highlight a slightly different part of the point that was made, or the question that was made, which was the importance of public engagement and the importance of public confidence and what happens. So, one part of the framework we haven't talked about today, but we have talked about in previous meetings, is how essential it is in the research, both pre-event and post-event, to start with community engagement, so that at each stage of it, it isn't something where if there is an event that the public and their perception of the government is that it is a feeling rather than an understanding and engagement in the process throughout from now until an event, in the unfortunate case where that could happen, and everything that follows. So, I think there was a different point that is in there worth highlighting and shows importance in our framework of fleshing that out as to what we mean, and how important it is from now, as soon as things happen from today going forward, that there is community engagement in the process itself and community buy-in the process that happens.

DR. GUTMANN: Good, that's a really important point. Any other comments or questions before – Lonnie, yes.

MRS. ALI: Christine, were you talking about post-event scenario or pre-event scenario talking about acceptable risk as opposed to minimal risk? I just --

DR. GRADY: I didn't specify.

MRS. ALI: You didn't?

DR. GRADY: Minimal risk has a regulatory definition and its controversial and people disagree about what falls under that rubric, but I think we have been talking about, I guess, more in the context of pre-event studies, doing enough research that we can, I think the word "make minimal" has crept in there little bit, make it minimal, and that doesn't make sense to me. The

more research you do, the more you know what the risks are and can decide whether they are acceptable or not.

DR. WAGNER: Yes. In fact, can I follow-up on the clarification, you can keep your microphone on, I want to hear from you on this. I think you are precisely right, and everyone agrees, we are not talking about making something minimal. One could determine whether or not it was minimal. Where I was confused was, your-- the way you use the word "acceptable risk" because my understanding has been that this has been all about acceptable risk and minimal risk is acceptable in one circumstance and some increment above minimal risk may be acceptable in other circumstances, but acceptable is what we have been talking about all along. That is how I've understood it.

DR. GRADY: I guess I am not 100% sure that I think we have to limit pre-event testing to only minimal risk.

DR. WAGNER: For it to be acceptable?

DR. GRADY: Yes.

DR. WAGNER: We better talk about that, I think that is where we are now.

DR. GRADY: And I don't know if that is what the commenter was raising either, to say no pre-event research unless its minimal risk is a pretty strong statement.

DR. WAGNER: I think that is where we are now, we ought to talk about that.

DR. GUTMANN: On the question of making -- it takes, making out, if you want, it is designing protocols that would minimize risk, okay. And that's what the --

DR. GRADY: Well, I -- I agree with that.

DR. GUTMANN: For example, we now know it's best we can and most knowledge is within, at most, the 90% confidence interval. We now know that if we went ahead, we're told, and we have to accept by experts that if research went ahead with the young children, it would be more than a minor increment over minimal risk, and that is unacceptable.

DR. GUTMANN: And that --

DR. GRADY: Can I say something about that?

DR. GUTMANN: Yes.

DR. GRADY: Maybe.

DR. GUTMANN: Of course.

DR. GRADY: Depends what I was going to say.

DR. GUTMANN: No, (laughs) my sentence was in the middle. But that is okay. You are welcome to interrupt me.

DR. GRADY: My understanding of that determination was because there are no data in little kids and so, the idea of collecting data in incremental way to determine how we can predict whether it's more than minimal risk or more than a minor increase over minimal risk, all that makes sense to me. I also think it is very important that it does make sense that we could find ways in incremental research to minimize risk. But that is still different than whether or not it ends up being minimal by most people's lights.

DR. GUTMANN: Correct. And remember, we are talking about pre-event research on children who do not stand to directly benefit from it for a totally indeterminate risk. So, it is really important to its ethical acceptability to maintain that at minimal risk. Now, there is minor increment over minimal risk again depends on how one defines it, but that's at the upward bound, no significant threat to the health or wellbeing of children.

DR. GRADY: So then that is minimal, not by its regulatory definition.

DR. GUTMANN: in the report we're going to have to get into the regulatory definition, but I'm not proposing to change the regulatory definition of minimal risk, especially in a situation where children do not stand to benefit directly and there is no -- we cannot know what the probabilities of an attack or incident are, and the government is not urging us to do, has not urged us to issue this report quickly, so there is no sense of imminence here, I think it would be, I will just go on record, I think it would be significant mistake of this Commission, to which I would not be party, to open the door to expanding the risk that children can be subject to in research, in a circumstance where they do not stand to directly benefit and there is not an imminent risk, an imminent threat, excuse me, an imminent threat. Dan.

DR. SULMASY: Yeah, I think I was perhaps responsible for introducing the infelicitous term "use or make", so I think what I would say is I think along the lines of what you were saying Christine that, the ideal that we would have would be by doing dose escalation or age de-escalation that the -- because by definition, if we don't know, have any information that it is more than minor increase over minimal risk that our hope would be by discovering that if the risk is low in an older age group that we would, on the basis of that information, be able to determine that the next increment would be a minimal risk study. That would be the aspiration. That still does leave open the question, what if it happened that it was more minor increase over minimal risk, would we allow it to go forward? And like you, I'm not prepared to say that I would absolutely rule out a sort of minor increase over minimal risk, and, as precluding a pre-event study even if it were done in the safest way with age de-escalation, but I certainly don't want to go to the level of saying we would allow healthy children to undergo liver biopsies or have a significant risk of losing limbs, et cetera, in those kind of studies.

DR. NELSON: So, I think the flexibility in our discussions on this point is probably given by the definition of imminence or high level threat using, Alex's, probably, the way he thinks. I think that gives us the ability to have a potent response to look at in a situation of imminence. If the United States government leader were to declare there is an imminent threat, then that would allow a different approach to pre-event research that we've already discussed. I think, some of us are coming into scratching our head like this. I'm an HIV vaccine researcher, and we've had panel discussions of plenty of pediatric vaccine researchers and this is done, we do vaccine research in children all the time, but the difference here is that, if the government is in the position to not be able to tell us that the risk of an attack and therefore the benefit to exposed

children, in this case, exposed to research can't be defined, therefore we just have to assign it as zero, then I think that provides one ethical bright line. I think that in a post-event, we being having lots of discussion this morning about that. I think where you have the link between them is that, if the government were to then say well, actually the risk is higher, at this point in time, I think that would open the door then to consider pre-event research in children with minor increment over greater than minimal risk. Basically pushing it into post-event column.

DR. GUTMANN: I am going to adjourn for lunch because we have to reconvene at 1:00, so we will reconvene at 1:00 promptly. Thank you all very much.

(lunch break) --