U.S. FOOD AND DRUG ADMINISTRATION

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OFFICE OF THE COMMISSIONER

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PEDIATRIC ETHICS SUBCOMMITTEE
of the
PEDIATRICS ADVISORY COMMITTEE

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2nd MEETING
"Precursor Preference in
Surfactant Synthesis of Newborns"

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TUESDAY,
JUNE 28, 2005

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The Advisory Committee met at 8:30 a.m. in Room 1066 of the Food and Drug Administration, 5630 Fishers Lane, Rockville, Maryland, DR. ROBERT M. NELSON, Chair, presiding.

PRESENT:

ROBERT M. NELSON, M.D., Ph.D., Chair
P. JOAN CHESNEY, M.D., Member
MICHAEL E. FANT, M.D., Ph.D., Member
JILL LEVY FISCH, Voting Patient-Family Representative
ALAN FLEISCHMAN, M.D., Voting Consultant
ANGELA HOLDER, LL.M., Voting Consultant
MARK HUDAK, M.D., Voting Consultant
PAULA KNUDSON, Voting Consumer Representative
MARY FAITH MARSHALL, Ph.D., Voting Consultant
RONALD RUBENSTEIN, M.D., Ph.D., Voting Consultant
KATE SHAFER, LICSW, Voting Patient-Family Representative
BILLIE LOW SHORT, M.D., Voting Consultant
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

PRESENT FROM FDA:

SARA F. GOLDKIND, M.D., M.A., Office of Pediatric Therapeutics, FDA
DIANNE MURPHY, M.D., Director, Office of Pediatric Therapeutics, FDA

PRESENT FROM THE HHS OFFICE FOR HUMAN RESEARCH PROTECTIONS:

BERNARD A. SCHWETZ, D.V.M., Ph.D., Director, Office for Human Research Protection, HHS
KEVIN A. PROHASKA, D.O., Office for Human Research Protections, HHS

ALSO PRESENT:

SARAH FRANKEL, Ph.D.
AARON HAMVAS, M.D.
JEFFREY A. WHITSETT, M.D., Ph.D.

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

(8:34 a.m.)

CALL TO ORDER, INTRODUCTIONS

CHAIRMAN NELSON: I would like to welcome everybody to the second meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee. And throughout the course of the morning, you will hear more from folks about the process.

But the first order of business is for each one of us to introduce ourselves. I'll just start to say I'm Robert Nelson. I'm a pediatric critical care physician at Children's Hospital, Philadelphia and am a member of the Pediatric Advisory Committee and chairing the subcommittee.

Why don't we start with Jill and each introduce ourselves. The microphone, you press the button. The red light comes on. And then you can talk. And since it's being recorded, I encourage everyone to remember to press their button.

MS. FISCH: Good morning, everybody. I am very happy to be here. My name is Jill Fisch. I am the National Director of Education and Awareness for the Save Babies Through Screening Foundation. And I look forward to working with everybody on this issue.

MS. SHAFER: Good morning. My name is

Kate Shafer. I am here as a patient and family representative. I am a licensed clinical social worker with a 20-plus-year history, work history, in pediatric hospital settings. I am currently the President of the Association of Pediatric Oncology Social Workers.

MS. KNUDSON: I'm Paula Knudson from the University of Texas Health Science Center in Houston. And I am an IRB person. And I have been the IRB administrator for 29 years.

MS. HOLDER: I'm Angela Holder. I'm Acting Director of the Center for the Study of Ethics and Humanities at Duke. And I'm a lawyer.

DR. MARSHALL: And I'm Mary Faith Marshall. I'm a bioethicist. And I'm at the University of Minnesota in a new position: the Associate Dean for Social Medicine and Medical Humanities.

DR. RUBENSTEIN: I'm Ron Rubenstein. I'm a pediatric pulmonologist and Interim Chair of the IRB at Children's Hospital of Philadelphia.

DR. FLEISCHMAN: I'm Alan Fleischman. I'm a pediatrician, neonatologist, and I do bioethics.

DR. HUDAK: Mark Hudak. I'm a neonatologist at University of Florida, Jacksonville.

DR. CHESNEY: Joan Chesney. I'm a profess of pediatric infectious disease at the University of Tennessee in Memphis and Director of Academic Programs at St. Jude Children's Research Hospital. And I'm also Chair of the Pediatric Advisory Committee.

DR. JOHANNESSEN: Jan Johannessen. I'm the Executive Secretary for the Pediatric Advisory Committee and the Pediatric Ethics Subcommittee.

DR. FANT: Michael Fant. I'm from the University of Texas Health Science Center in Houston. I'm a neonatologist and biochemist. And I'm on the Pediatric Advisory Committee.

DR. SHORT: I'm Billie Short, Chief of Neonatology at Children's Hospital here in Washington and professor of pediatrics at the George Washington University.

DR. PROHASKA: Good morning. My name is Kevin Prohaska. I work with the Office for Human Research Protections. And I'm the Children's Research Coordinator.

DR. GOLDKIND: And I'm Sara Goldkind. I'm the bioethicist at the FDA.

DR. MURPHY: I'm Dianne Murphy. I'm a pediatrician and the Office Director of the Office of Pediatric Therapeutics at the FDA.

DR. SCHWETZ: Good morning. I'm Bernard Schwetz, the Director of the Office for Human Research Protections.

CHAIRMAN NELSON: Thank you, everyone. And now Jan will read the meeting statement.

MEETING STATEMENT

DR. JOHANNESSEN: Good morning. "The following announcement addresses conflict of interest with respect to this meeting and is made part of the public record to preclude even the appearance of such at the meeting.

"The topics of today's meetings are of broad applicability. And unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their interests as they may apply to the general topics at hand.

"The Food and Drug Administration has determined that no potential conflicts of interest exist. The FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the Committee, these potential conflicts are mitigated.

"With respect to participants, we ask that in the interest of fairness, they address any current or previous financial involvement with any firms whose product they may wish to comment on." Thank you.

We have the open public comment scheduled for 11:00. And I would just remind everyone to turn their microphones on when you speak so that the transcriber can pick everything up.

Thank you.

CHAIRMAN NELSON: Thank you.

So the first item on the agenda is a description of the expert panel process. And I believe, Sara, are you going to be going first?

SUBPART D EXPERT PANEL PROCESS

DR. GOLDKIND: Good morning. We're very excited to have you all, such a distinguished panel, here to deliberate this particular compelling protocol. And what I wanted to do was take a few minutes to go over.

I know that some of this is old hat for some of you and new for some of you. I wanted to go over the process, discussion of how this particular subcommittee functions, and how the deliberations that occur today end up in a final determination by the Commissioner and ultimately by the Secretary of HHS.

Dr. Schwetz and I are going to share this presentation. And if time permits, we would be happy to take questions. If not, if you have questions, you can approach us during our scheduled breaks.

So, first off, both HHS and FDA have regulations called Subpart D, which are additional safeguards or protections for children as part of clinical investigations or research.

And those regulations have four different categories. And I put the numbers 46.404 and 50.51 because even though they say the exact same thing for FDA and for HHS, they're numbered differently.

The first three categories are categories that the IRB is authorized to allow a protocol to proceed under without a referral. If the IRB feels that it can approve the protocol under one of the first three categories, but it feels that the research represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, it can forward this protocol to the federal agency that has jurisdiction over the protocol, such as the HHS if it's a federally funded or conducted protocol, or FDA if it involves FDA-regulated products. And if it involves both of those aspects, then it's a joint referral, such as we

have here today.

Now, some of the considerations that are potentially open to this Subcommittee today are to evaluate the determination of risk; the assessment of benefit; whether there are suggested modifications to the protocol itself; whether there are necessary modifications to the protocol; whether there are suggested modifications to the consent documents; the parental permission, -- in this case, there is no assent process since it involves neonates, but that would be a consideration if it involved older children -- whether there are necessary modifications to those informed consent documents -- and then there are specific questions that you're asked to address today; they're in your packets -- and, additionally, to assign an approval category, one of the Subpart D approval categories that we have just breezed by; and whether there are any other additional pertinent issues that you might want to deliberate. So those are just some general considerations that you might want to incorporate into your discussions today.

Now, what are some of the possible recommendations that the Pediatric Ethics Subcommittee can make to the parent committee, which is the Pediatric Advisory Committee?

It could recommend that the protocol proceed because it feels that the protocol actually falls under one of the first three categories of Subpart D or it could recommend that the protocol proceed with modifications because those modifications are important and would allow the protocol to then be classified under one of the first three categories of Subpart D or it could recommend allowing the protocol to proceed either with or without modifications because it satisfies the 50.54 or 46.407, which we'll talk about in a minute, or it could recommend that the protocol not be allowed to proceed, providing specific reasons for that decision.

Now, if the Pediatric Ethics Subcommittee feels that the protocol falls under 46.407 or 50.54, it has to satisfy three particular conditions. And those conditions are that the research again presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, that the research will be conducted in accordance with sound ethical principles, and that adequate provisions are made for soliciting the assent of children and permission of their parents or guardians, as set forth in other sections of the regulations regarding

informed consent.

Now, it's also possible, just to go back for a minute, that the Pediatric Ethics Subcommittee will feel that two particular categories for Subpart D approval are applicable because you have two different populations that you're looking at. You're looking at the control group, and you're looking at the interventional group. So two particular categories might apply, one for each of those groups.

Now I am going to turn the rest of the presentation over to Bern.

DR. SCHWETZ: Good morning again. And thank you, Sara.

As you go through the deliberations today and you're concerned that this is a joint review of OHRP and the FDA, you needn't be concerned that you're looking, really, at two different sets of regulations because, in effect, you're not.

The point here is that the regulations that the FDA works through and the regulations that we have as the authority for OHRP are comparable. And that needn't be a point of discussion and concern for you today.

Look at the science and the protocol, not whether or not there are subtleties in the regulations

that would prompt a decision in one case that's different from the other.

So what happens after today's meeting? By the end of the day, before tomorrow noon, 12:30, the Chair will be responsible for organizing the recommendations that come out of this meeting today.

So Skip will be taking the recommendations from your meeting today to the Advisory Committee meeting tomorrow and will be delivering and speaking on your behalf to represent what you recommended about the disposition of this protocol.

So then what happens after that is that the recommendations of the Advisory Committee, the Pediatric Advisory Committee, will be taken by the FDA to the Commissioner and whatever briefing and other information it takes to allow the Commissioner to make a decision there. So the Chair's summary and the recommendations from the Advisory Committee will be taken to the Commissioner for a decision within the FDA.

Then that decision by the FDA, together with the recommendations from this Committee and from the Advisory Committee tomorrow, that will be packaged and taken to the Assistant Secretary for Health within the Department of Health and Human Services. And OHRP

is the transmittal mechanism for that particular decision. So then the ASH, the Assistant Secretary for Health, will make a recommendation on behalf of the Secretary.

The choices that they have within HHS for the disposition of this, remember, they're the ones who are going to say to NIH whether or not this work should be funded. That's why it comes up to the department.

And depending on your recommendations and what you put to them, the ASH might conclude that the research, in fact, is satisfied through one of the other mechanisms and should be taken back to the IRB for review and potential approval as a 404, 405, or 406-level decision or the Secretary may support that the research should be approved under the 407 mechanism.

And the recommendation would, therefore, be that it should be funded having undergone this review of the expert panel and the solicitation of input from the public or the decision should be that the research should be supported under 407, but there are modifications to the protocol that are required or the decision could be that this shouldn't be funded at all. And sometimes that is the recommendation of the

ASH and the Secretary to NIH, not every time.

But I think all of these choices have been played out through one protocol or another. So it isn't that this is just a theoretical exercise and the same thing happens every time.

So if you have questions, as Sara said, if we have time to answer them now, fine. If not, catch us any time during the day to ask how this process is really handled by OHRP and by the FDA.

But, again, thanks for your willingness to help with this.

CHAIRMAN NELSON: Thank you, Sara and Bern.

I might say for those of you who don't know me, Skip is my nickname. So that's who he was referring to.

Are there any particular questions, at least about what we have heard? I mean, we are going to be going into more detail over time about the IRB categories and the like for those of you who are not familiar with it as we deliberate. But let me see if there are any questions people might have for Sara or Bern as we get started.

(No response.)

OVERVIEW, CHARGE TO PANEL AND FINAL

OUTCOME

CHAIRMAN NELSON: Okay. A couple of comments in terms of overview and charge and final outcome. People might wonder why an FDA committee, basically even if something is used in a way that is approved or labeled basically an FDA-regulated product is involved in this research.

I think many IRBs are often confused about that, thinking that it is only when you have investigational devices or drugs that the FDA gets involved, but, in fact, they do have jurisdiction over any clinical investigation that involves an FDA-regulated product, even if it's being used on label.

As far as what we hope to achieve by the end of the day, ideally I should be able to summarize for you exactly what you have said about this protocol. And we will decide together whether that would be approval under one of the four categories absent any conditions, approval under one of the four categories with conditions, -- and then I am going to push people to say, "Well, is that a condition that you would absolutely require or just something you think would be nice for them to do?" and divide it out that way -- or that we would recommend disapproval and

going through each of those conditions.

So at the end of the day as we go through that, we will hopefully identify that for you and then have each one of us comment on that. And then I will be able to summarize that for the Advisory Committee.

For those of you who don't know that the FDA process, only an Advisory Committee can recommend anything to the Commissioner or to the Secretary. So we actually advised the Advisory Committee. But I would hope that our deliberations are complete and compelling enough that there is minimal modifications as we get to that next step, which is partly why we have a number of people from the Committee actually present at this process.

So that's what I hope to achieve by the end of the day. And we'll see how it goes. Any comments or questions before we jump into the content?

(No response.)

CHAIRMAN NELSON: So our first presentation is from Dr. Whitsett from Cincinnati Children's, who is going to provide an overview of surfactant to basically bring us up all to hopefully a common scientific basis to then launch into a specific discussion of the protocol and of the issues.

OVERVIEW ON SURFACTANT

DR. WHITSETT: Good morning. I'm delighted to be here and hope that my comments will be useful for your deliberations on this important protocol.

I am a neonatologist. I have practiced in the intensive care unit for about 30 years. And I also direct a laboratory involved in basic research in surfactant biology and have been coated with this lipidy slime for about 25 years, during which we identified and isolated many of the genes and proteins involved in how surfactant works. So I live and breathe surfactant biology, and I hope to share a little bit of that with you.

What is behind all of this is really a revolution in care that has occurred during that 30 years in which we began to understand how to take care of pre-term infants who had respiratory distress syndrome or hyaline membrane disease.

Most of the children we are talking about this morning didn't survive. And we weren't even allowed as residents to place them on ventilators or to try to support them if they were less than 1,000 grams. Now most 1,000-gram babies survive. Ninety-five to 97 percent of those survive and go home, most of those attacks.

It's about four million births in the United States. And about 11 percent of those are pre-term. Of those, that gives us 40,000 infants. Approximately 1.3 percent are actually less than 1,500 grams. Those infants represent a severe burden of morbidity and mortality.

As we begin to get smaller and smaller, approximately 32,000 in the United States are less than a kilogram. Most of these infants have a prolonged period of hospitalization. They often will have -- 60 percent, 66 percent of those less than 1,500 grams will have a prolonged period of instability, requiring intensive care.

About 66 percent will present with acute respiratory distress syndrome or surfactant deficiency and require intervention in the first few days of life that is now quite life-saving and requires ventilation and administration of exogenous surfactant that contains lipids and proteins.

About 24 percent of those children undergo a prolonged disease process called bronchopulmonary dysplasia. This is defined as infants who at 36 weeks gestation continue to need oxygen, can't leave the intensive care unit, require special feeding, are high risk for many of the complications of nutritional

problems, infections, drug exposures that can exacerbate their stay in the hospital. Mortality continues to be significant in this group.

So we have had a revolution in the care of early RDS. Almost all of these babies died in the first two or three days. Now we routinely survive. But we're challenged then by at least a month or two of intensive care unit with nutritional support.

And after 30 years, I simply am solidly aware that I don't know half the time what I am doing in terms of nutrition and support of these chronic children. So knowledge to make this field advance is absolutely required.

This is extraordinarily expensive. The average tiniest of our babies at 24 weeks gestation will cost about a million dollars to go home. And the first year of care with recurrent visits to the hospital and supportive care can be extraordinarily expensive.

The problems are twofold: respiratory distress syndrome or acute deficiency of surfactant, which we now handle by careful ventilation and replacement, which only lasts for about 48 hours. After that, the baby is on his own and has to synthesize his own surfactant material.

That period of synthesis and recovery leads to a disease called bronchopulmonary dysplasia, which is a very severe form of lung disease with interstitial remodeling, malformation, actually dysplastic repair of the lung. It leads to oxygen requirements for many of these children for even the first year of life.

This is very age and weight-related. And as you can see on this chart, survival with BPD -- that means they got out of the intensive care unit but require continued support -- is very gestational age-dependent. And the smallest of preemies -- and this is 400 to 600 grams -- who are now surviving, more than half of those infants have severe respiratory complications that continue; as you get larger and larger, -- that's per 100-gram body weight -- up to about 1,500 grams, the morbidity of that chronic disease.

It doesn't mean we know how to take care of those larger babies who are doing well. It means that they aren't so sick. It doesn't mean that we are optimizing their care. It's just that they aren't so sick that they don't die and they don't require prolonged hospitalization. But whether we're giving optimal care and optimal nutrition, even in the larger

babies, is not clear to us.

This is an X-ray of a baby with severe hyaline membrane disease before surfactant replacement. And it shows an endotracheal tube in place and very severe opacifications of the lung with air bronchograms in a reticulogranular pattern, which is rarely seen today because we give surfactant replacement and are able to rescue this early form of lung disease.

This is a tiny baby's lung seen histopathologically circa 1976, when I was a fellow back in Cincinnati. And it's completely collapsed lungs with the only air in this baby's lungs in the tracheal-bronchial tree and not reaching the distal parts of the lung because the lung is completely collapsed and the baby can't move his chest.

The normal lung, seen here, is stained with one of the surfactant proteins that shows you the black dots, which are the type II epithelial cells, which are the synthetic engine that will turn substrates, both glucose and stored glycogen and fats that the baby might take up from nutritional support and from his body, to generate the surfactant lipids that are required to maintain reduction of surface tension in the alveolaris.

This is absolutely critical. We have this going on in our lungs all the time. If we lose our surfactant this minute, I won't be able to breathe for about five minutes. And you won't be able to reinflate my lungs unless you give me surfactant back.

So once you're burn, you have this material in your lung. You need it all the time to breathe. And the loss of it causes acute respiratory distress syndrome in adults. The lack of it because of prematurity causes the syndrome in pre-term infants.

Normal lung looks like this. It's air-filled, wonderful interaction between the gases in the terminal saccules and the capillaries in the lung tissue that allow for carbon dioxide and oxygen exchange.

In the absence of surfactant, the lung looks like this with hemorrhage, collapse, and the baby can't be ventilated. The problem is water molecules simply love each other. And a drop of water on the waxed surface makes a bubble, and it rises up over the top of it or it rises up in a straw. And that's related to water molecules adhering to each other because they just like to be around each other. And we're not at boiling temperature. So we don't

have gases flying off into the surface.

And at the air-liquid interface covering the entire surface of your lung, which is about the size of a squash court, the water molecules come into direct contact with gasses that then lead to collapsing forces that are very difficult to overcome.

Essentially imagine a plate glass window the size of this area here, water between them, then put them together, and then try to get them apart. And that's the physical problem of being able to breathe with no reduction of surface tension.

So we have evolved a very complex system, a biochemical system, that creates a new phase at the air-liquid interface composed of lipids. Those lipids, like an oil spill, sit at the surface of the air-liquid interface and reduce surface tension or block those unequal, unopposed forces generated by water molecules at the air-liquid interface.

To do this, we couldn't put gasoline under the -- during evolution, we had many solutions. We could put soap on our lung. We could put gasoline or oil. None of those are really compatible with long-term survival. So we've adapted the synthetic machinery of placing lipids at the air-liquid interface.

These lipids are miraculously structured by a number of proteins and the kinds of lipids that they're composed of. And this is what they look like by electron microscopy, newly secreted into the lung of a newborn mouse lung.

The onionskin are lipids. Ninety percent of that is lipids. They uncoil as it hits the extracellular space and forms material called tubular myelin. That tubular myelin forms a raft of lipid material that is now available minute by minute, second by second to go to the surface of the lung.

So we've got to keep the small airways open during the ventilatory cycle. If they collapse, we can't breathe and have oxygen exchange. And to do that, the type II epithelial cells seen there, the yellow cell, makes those lipid-rich lamellar bodies, secretes them onto the surface, and creates a surface film that lines second by second every time you take a breath, collapsing and reforming as you breathe dynamically to keep lipids at the air-liquid interface.

The composition of surfactant is well-known from the '60s and '70s. And it's predominantly lipids. It's good fat, as opposed to all of the bad fat circulating in our bodies. And

it's regulated in exactly a complex way as the lipids in our cholesterol and our VLDL, et cetera, in our bloodstream. We have begun to understand that over the last two or three decades.

So it's very expensive for cells to make all of this lipid. It's phosphatidylglycerol and dipalmitoylphosphatidylcholine, or phosphatidylcholine. That's the green in our piechart. That material is uniquely unsaturated. These aren't like lipids in the normal membranes of our cells or in our bloodstream. These are special lipids that have had remodeling of their acyl chains so that they pack differently.

If you have double bonds in your acyl chains, you kink and you perturb your neighbors. And if you perturb your neighbors too much, the water molecules can start talking to the surface of gas.

And so we have to have lipids that all get in line and line up very rigidly and don't allow interface between the air and the liquid. To do that, we have made a remarkable stuff. It's dipalmitoylphosphatidylcholine. It's enriched only in these little cells and only in the lung. The rest of your body could give a hoot about what kind of lipid you have or how you make it.

In the lung, it's very important that these things pack and line up. If you have the wrong kind of lipid, it won't work well. So it's mostly fat and a few proteins. The proteins that are critical for that are SP-B and SP-C. And that's the material that's in our surfactant that we give exogenously. But after two or three days, the baby has to make his own lipid and proteins SP-B and SP-C.

How they do that, what substrates they use, how they make all that fat, what's the preferential utilization of substrates for optimizing the production of the lipid component or maintaining the protein components is very little known. And in the long run, the neonatologists will need to understand the biochemistry of this in the intensive care unit in the baby as we take care of them. And we'll include not just the lipids that we're talking about today, but in the future the other components of surfactant that will be required to maintain optimized care.

This is an electron micrograph of a pre-term lung. In this case it's a mouse that shows the immaturity of the type II cells that cause RDS. And one sees on your right side the cells here. They are completely in the surfactant complex.

This is lamellar body being secreted in the air space. In the normal lung, -- and this is a pre-term lung full of glycogen -- it wants to make surfactant, but it hasn't learned -- do I have a pointer? Thank you. These are secreted into the air space, synthesized from the glycogen that's generated by the accumulation and synthesis from substrates prior to birth.

After birth, that glycogen is completely mobilized. It's no longer available for making surfactant. And the baby becomes dependent upon the uptake of substrates that will be required for the ongoing manufacturer of the lipid particles that will be required for breathing.

So the type II cell is going to take up -- initially it uses up its glycogen and synthesizes the phosphatylcholine from glycogen, thereafter birth takes either palmitate, acetate, or other carbon sources, or synthesizes from glucose substrates that allow the ongoing manufacture to stop secreted in the air space. And it forms this multi layer that reduces surface tension of the air liquid interface. This has to be there all the time.

So initially we help the baby generate its own after two days. He's on his own. And they go

through a prolonged period of up to a month or two of instability and lung dysfunction, during which we need to guarantee adequate substrate and production of surfactant during that.

We don't give surfactant replacement after the first several days. The baby is on his own. And we need to understand what is the biochemistry and biology of making this material to maintain lung function.

It's recycled. And it's reutilized in a very extent. So what do we know about the biochemistry and the synthetic and pool sizes recycling and biology of surfactant in the airway?

There's a large surfactant pool that we all run around with. And before birth, this pool is amazingly increased, approximately 100 milligrams per kilogram body weight in a full-term baby who is ready to take his first breath. You and I do fine with about four milligrams per kilogram. There are 25-fold more in a new baby.

Mother Nature takes getting both very seriously and wants to make sure the first breaths really work. To do that, we have this huge pool size.

Pre-term babies' pool size is very low. So they're lacking the surfactant pools and,

therefore, are dependent the first few days with what we give them. So we give surfactant back to them to increase this pool size.

Because of the active recycling of surfactant, the surfactant that we give stays there a long time. We need to understand what increases or decreases the turnover of surfactant from the lung because our medications, our therapies might be breaking that pool down faster than it should be.

Pre-term babies have abnormalities in their epithelial barriers and have fluid in their lungs. It leads to pulmonary edema, often complicated by the ductus arteriosus, which floods the pre-term baby with fluids, which inactivates surfactant. And we don't know how to optimize therapy to maintain active surfactant and to keep it from being degraded.

The maintenance of the surfactant pool size is critical for minimizing sheer forces and damaging influences of our ventilators and the pressure and oxygen that we give to support the babies during this critical time.

So that leads to alterations in lung structure that causes inflammation, alterations in tissue structure and function that then influences both the severity of RDS as well as the outcome in

terms of healing the lung during the last few months of their stay in the hospital.

We know that giving surfactant back exogenously dramatically and quickly improves surfactant function. This is a pre-term lamb in which it is about a 24-week gestation lamb, comparable to a very severe immature baby with very little lung volume. It takes a lot of pressure to open the lung. And when the baby breathes out, the lung completely collapses.

If you simply give surfactant back, air fills the lung. There's a large lung volume. And at the end of expiration, the lung stays inflated like a normal adult lung. This just shows the absolute critical requirement for the presence of that surfactant material in the air space.

This has led to the application routinely now of replacement surfactant by a number of preparations that leads to a decrease in mortality and morbidity related to acute RDS, but it hasn't changed the incidence of bronchopulmonary dysplasia or the long-term dysfunction of lung dysfunction that these babies undergo.

In fact, it's increased the numbers of survivors and, therefore, increased the burden of care

and our need to then support these tinier and tinier babies during the prolonged period of their repair process.

So how do we get the surfactant lipids and proteins into the air space? We know very little about it, and there are only a few human studies. We know some from animal studies. But, to point out, there are no animal models, viable long-term animal models that truly mimic the problems we have in the intensive care unit.

There is an intensive care unit for baboons in San Antonio. There are a few experiments with prolonged ventilation of sheep, lambs at the time of birth, but we don't have any easily maintainable models to study the details of both nutrition and surfactant homeostasis during this prolonged month or two recovery time that our babies undergo. We simply can't keep the animals stable for that period when they are this ill.

Most of the studies we have are using radiochemical tracers in animals. What we know from those studies, both in rodents, sheep, rabbits, is that a precursor injection of either lipid, lipid precursors, or glucose that is taken to the type II cell in the lung, taken up by the cell and the

phosphatylcholine, in this case saturated phosphatylcholine, emphasized by the lung cells, predominantly the type II epithelial cells.

Synthesis is relatively slow. This occurs over a prolonged period of hers. We can label the time of appearance by sampling the endotracheal tube or if it's an animal model, we can sample the tissue and quantitate the amount of uptake of different precursors in how they're taken to the cell and made into the lipid component. Then we can isolate.

We certainly can't access the tissues in babies. We can only access what secreted into the air space and what is removed from the body compartment after an injection. And we can't use radio tracers to do that.

Synthesis occurs relatively slowly. And then once it's secreted into the air space, we can monitor that by removing material and sampling that material. We can't do it quantitatively because we can't wash the entire lung out without jeopardizing the baby. So all we can do is take a sample of that material that contains the synthesized, newly synthesized lipids, and assess how much of any kind of label was incorporated compared to the amount of total material that we can measure from that sample.

And we can follow the disappearance of that material over time. And what we see here is an extraordinarily slow -- this is for most animals -- disappearance curve, which suggests that it is being actively reutilized.

What regulates that, what determines how much is catabolized and removed by macrophages, taken up by the type II cell, catabolized, broken down into the components and used for energy, or actually taken back up, recycled, repackaged in the lamellar body, and then sent back out into the airway is really unknown.

And if we understood each of those compartments, what regulates those compartments, how can we optimize maintaining the amount of surfactant in the airway, we could perhaps design more rationally our treatments, both nutritionally and for the lung.

So we have a sense of synthesis and its clearance. And we can only do that by assessing what is in alveolar washes or by sampling little aliquots of alveolar material, as is possible in humans.

The amount of surfactant, again, is very high in the normal newborn infant, about 100 milligrams per kilograms, getting ready for the first breath. And in the pre-term, it's somewhere between

zero and ten milligrams per kilogram depending on your gestational age. And in the adult, it's only four.

So there is a particular challenge in being born. And that has to do with the permeability of the lung, the inactivation of surfactant, pulmonary edema, and the relatively low pool size. There may be enough for the first hours, but the low pool size in the pre-term infant is rapidly used up.

The synthetic rate is relatively slow and can't restore the pool size. And so essentially the baby runs out of gas, and we have this honeymoon period where the child might be quite stable for a few hours. But then, inexorably, they will run out of surfactant and become sicker and sicker over the first hours and days of life.

This also opens post-natally in the first month of life. They will become stable. They will have a minor infection, a difficulty with a ductus arteriosus. And, all of a sudden, surfactant doesn't function adequately; the baby again runs out of gas; the synthetic rate is very, very slow; and the baby then has respiratory failure once again. And many of these babies go through these terrible cycles of requiring more and more support that leads to more and more chronic lung disease.

So the pool size, how much surfactant you have, directly correlates with what your PCO2 is. That's how bad your lung is working. So if you take a very pre-term baby at -- this is a lamb; it would be the same probably in humans -- very early gestation, the pool size of saturated PC is very low. And the PCO2 is very high. These are lethal levels of PCO2.

At a certain level of pool size, lung function is restored. And more doesn't help you, but having an adequate pool size guarantees your ability, then, to reduce PCO2 and have ventilatory, respiratory function. So the amount of lipids in your lung is really an important determinant of how well your lung is going to work.

One of the most dramatic differences between pre-term babies and adults is how long the surfactant lipids stay in the airway under normal conditions, although we don't have any sense of what the turnover and clearance are in the injured lung or the baby's lung with BPD.

The appearance of labeled surfactant in PC is seen here in both lambs, baboons, and a small amount of data from pre-term infants. What one sees is the prolonged period it takes after precursor injection to get the surfactant synthesized and into

the air space.

It's an extraordinarily slow process. It takes days to build up your surfactant pool. In fact, it's about a pool size change of something about 4.7 percent per day. And so if you're one or two and you need to go to 10 or 20, it's going to take you days, not hours, after the precursor uptake and synthesis and secretion, days to increase your pool size. It's only four percent per day is increased in most of the babies studied with acute respiratory distress syndrome and in many of the animal models.

The clearance of surfactant from the air space is also very, very slow. This is pre-term baboons, pre-term lambs. And it just shows you the decay level. Once the surfactant that's labeled enters the tracheobronchial tree, it stays there for a prolonged period of time with a half-life varying between 24 and 48 hours. So once you get in there, if you have a normal lung, what happens in the ill baby or baby with infection or BPD is not well-known.

So it's cleared slowly. It takes forever to get the label in there. Knowledge regarding its biochemistry, preferred substrates, how much is from glucose, how much from other lipid substrate is very little known.

This is all occurring during a period in which we're unable to feed babies normally. Often they're unstable enough that we have to give substrate by giving them intralipid or by giving glucose and amino acid infusions to the baby.

Increasingly, we're trying to give milk and breast milk as early as possible, that many of the babies have a prolonged period of instability that requires the use of substrates that we really don't understand well.

We don't have many alternatives for intravenous alimentation. We only have a few preparations. They have uniquely enriched precursors so that they're enriched in fatty acids that aren't normal fatty acids that we're normally eating, but it's the only way at present that we have supporting nutritionally adequately.

So understand how those precursors are recognized, utilized by the baby to make surfactant is an important issue for us clinically.

So the summary of that biochemistry is that the type II cell is a synthetic engine. It has to put proteins and lipids into the air space. The lipids are very expensive metabolically to make. They come from glucose and other substrate stores, some of

which comes from recycling after administration of the surfactant, but that only is good for a couple of days.

Thereafter, it's dependent on uptake, mobilization of substrate stores, either from lipid or glucose, to generate the lipids and the proteins that have been put into the air space, some of which are degraded very slowly by the infant and some are recycled. So it's a very complex system. And we have very little knowledge regarding it.

Endogenous pool sizes are small in the pre-term infant. The synthesis and secretion are very, very slow, taking at least 70 hours to get half of that pool size. Catabolism and clearance are very slow in days. They're probably used as substrates after endotracheal administration. And there's a long-term requirement for ongoing synthesis in the first months of life that will impact on the care of the baby for a prolonged period of time.

Now, the intensive care unit is indeed a very complex place. I mentioned the nutritional complexities of not having normal nutrition and supplements for a longer period, but many other things we do in the intensive care unit or have happened to the baby can influence how lung development proceeds.

This includes infection that's led to prematurity, what we do in the resuscitation and delivery room, how we give and how much oxygen we give, whether the baby gets nosocomial infections, either sepsis or in the lung, and we use a number of drugs, including steroids, indomethacin, postnatal corticosteroids that have both anti-inflammatory effects but also profoundly influences the synthesis of lipids in the maintenance of surfactant from mustatis.

So as a clinician, I am intervening in many, many complex ways with a very vulnerable infant. And I have very little knowledge to go on. I don't know what's the optimal way to feed, when should I give these drugs, how safe are they. So we have a great challenge before us to optimize care in the coming years.

To my view, I need a clear knowledge regarding the biochemical pathways and the opportunities, both for therapy and for minimizing damage. As I continue I hope another 30 years of neonatal care in my career, I am solidly aware that I have a vulnerable baby with great complexities. And I need the knowledge that comes from biochemistry and physiology to optimize the care.

You all have to decide whether there are

risks involved in these protocols, but as a clinician, I feel strongly that I need scientific knowledge to optimize care for these babies. And that requires knowledge of how to feed the baby, what is the optimal way of providing care to maintain surfactant during the post-natal period.

Thank you very much. I hope that has been useful to you and would be glad to take any questions you might have. Thank you.

CHAIRMAN NELSON: Thank you.

If I could make a suggestion, we're going to have an opportunity to question Dr. Whitestt before lunch. And I think it would be nice if our questions are framed within the context of the specific protocol.

So unless there's a burning question right now, I would suggest we hear about the protocol. And then we can obviously invite Dr. Whitestt back for any other questions about the science and the background. Does that make sense? Okay.

So Dr. Hamvas, who is the principal investigator from Washington University, will give us an overview of the protocol under discussion. Good morning.

DR. HAMVAS: Thank you, Dr. Nelson.

BACKGROUND ON PROTOCOL

DR. HAMVAS: It's a pleasure and an honor to be a participant in this process, although when I first heard about it, I was unsure how much of a pleasure and honor it was going to be. I think that these kinds of deliberations are really going to be crucial in terms of us being able to really adequately move knowledge forward in our care of babies.

I must say I'm a neonatologist, first and foremost, and a clinician/researcher, secondly. The protocols, the studies that I am going to describe that we have already performed and that we are proposing now really emanate from similar frustrations that Dr. Whitestt has experienced in our care of these extremely premature babies.

We have improving outcomes, but, yet, I think we're getting lucky. I think we do well, but we really need to know considerably more than we do in terms of our care of these babies so that we can adequately take care of them and not only improve survival, which we have done, but, really, more importantly, decrease the morbidity associated with premature birth.

So over the next half-hour or so, I'm going to go over three major issues. Number one is

stable isotope methodology. That's the methodology that we're using in these studies. I'm going to provide a summary of our experience to date with these studies. And then I will spend most of the time on the specifics of the particular protocols.

So let's just talk a little bit about stable isotopes. Dr. Whitestt referred briefly to many of the studies that are performed using radioactive isotopes. Obviously those cannot be used in babies, but the basic tenet of stable isotope or isotope tracer methodology is that a tracer is a substance that is added to a system to interrogate one or more metabolic pathways. But the tracer must be indistinguishable from the naturally occurring molecule of interest or the natural substrates. So the tracer itself cannot perturb the system in any way. And that is one of the key assumptions in performing these isotope studies.

Now, stable isotopes, as opposed to radioactive isotopes, which emit radiation, stable isotopes are non-radioactive. And they are different from the natural substance in that they possess one extra neutron, but they do not undergo radioactive decay. They're stable.

This one neutron mass difference in a

substance is detectable with mass spectrometry, very sensitive techniques that have been available for many years and are getting better and better, extremely more sensitive.

These stable isotopes are naturally occurring. And I'll come back to that in a bit. And, as such, they're safe. And there's an extensive history of using these tracers to study carbohydrate, protein, fat, and energy metabolism, not only in older children and adults but in infants as well.

And some of these studies, in adults especially, go back to the 1930s and 1940s. So there's extensive experience with these. There's extensive experience in using these tracers in infants going back to the 1970s. So there's a wealth of literature in terms of using stable isotopes, especially to study metabolism and nutrition in newborns.

These are some of the naturally occurring stable isotopes in nature: hydrogen, carbon, nitrogen, and so on. These stable isotope that we are focusing on and that we utilize in these studies is a stable isotope of carbon.

The atomic weight of carbon, the natural molecular mass, is 12. The isotope with one extra

neutron for carbon, carbon-13, has a molecular mass of 13 and is present in nature in about one percent. One percent of all carbon atoms contain carbon-13. So we are made up of one percent carbon-13 at this point.

So carbon-13 is an abundant naturally occurring stable isotope. And this is the isotope that we take advantage of in performing these studies.

So let's talk a little bit about palmitate. Palmitate is the fatty acid. It's a ubiquitous fatty acid. And it's very abundant throughout the body, but it is most abundant, as Dr. Whitsett was saying, in the pulmonary surfactant. As a matter of fact, it composes approximately 60 percent of all the fatty acids in surfactant.

So surfactant is a unique molecule in that it is enriched in palmitate, palmitic acid. And so this is the molecule of interest that we are studying in our studies of surfactant metabolism in newborns.

Now, when we look at the palmitate molecule, there were 16 carbon atoms. And each one of these carbon atoms has a 1.1 percent chance to be a carbon-13 atom. The natural abundance of carbon-13 in nature is 1.1 percent.

So each of these carbons has a 1.1 percent change of being carbon-13. But when you look at the

molecule as a whole with 16 carbons and each one has a 1.1 percent chance, that means that ubiquitously and in nature and in the body, 17.6 percent of all the palmitate in our body has at least one carbon-13 atom attached to it.

And so this is a very abundant molecule that's already present in our body. When we perform our stable isotope studies, we're taking advantage of this by adding a little bit of extra carbon-13 labeled palmitate into the system so that we can trace its synthesis, secretion, and so on.

So here is a conceptual framework that we have been working with. And this reiterates what Dr. Whitsett was reviewing. Here is our surfactant molecule in general. This is the alveolar type II cell, where surfactant synthesis occurs in the lungs, and the plasma.

The palmitate is the primary precursor, primary component of the surfactant complex that we are looking at. And palmitate can be derived from several different sources. It can be derived directly from palmitate that is circulating in the plasma or it can be synthesized de novo from other sources, such as other cellular lipids, or from precursors of palmitate; that is, acetate and acetyl-CoA, which are

assembled together to ultimately form the palmitate molecule. Glucose fatty acids, amino acids also provide a substrate for acetyl-CoA that ultimately ends up in palmitate.

Now, for these stable isotope studies, then, we are taking advantage of these two metabolic pathways, these precursor steps to look at the synthesis of palmitate, either directly from uptake of palmitate from the plasma using a palmitate molecule that is labeled with four carbons that have carbon-13 or with acetate that only has one carbon that is carbon-13 and utilizing the differential molecular masses of these, we can interrogate these two pathways in surfactant synthesis.

Here is a chemical structure of dipalmitoylphosphatidylcholine, DPPC, the primary surface active phospholipid in surfactant, the choline moiety, a triglyceride backbone or a glycerol backbone and then two palmitic acid or two palmitate chains attached to it.

Now, when we use the stable isotopes, as I mentioned, we interrogating two different pathways. The first is a pathway utilizing acetate, in which we have one of the two carbon atoms in the acetate molecule labeled with carbon-13. It is ultimately

synthesized into palmitate, which contains any number of acetate building blocks, up to eight acetate building blocks, and may have one, perhaps two, and very rarely three or four of these carbon-13 labels in it. And it ultimately gets incorporated into the dipalmitoylphosphatidylcholine.

As I mentioned, the other pathway that we were interrogating is the pathway that is coming directly from plasma-derived palmitate. So we infuse a palmitate molecule that has four of these carbon-13 atoms. It gets incorporated into DPPC. And because of the mass difference between the four carbon-13 palmitate and the one carbon-13 palmitate, we can interrogate those metabolic pathways and understand where the surfactant synthesis, from which substrates it is being derived, and to what extent.

The general methods that we use for these studies, we use a 24-hour infusion of these 2 tracers. We obtain sequential blood samples during the infusion period. These samples are contained in conjunction with clinically indicated samples in these critically ill infants.

And we require up to 2.5 milliliters in 5 aliquots over about 27 hours. We can get by with less, and we do if the baby is not having blood drawn

that frequently. But at most, we will take five aliquots of 0.5 ml each for a total of 2.5 ml.

We obtain sequential tracheal aspirate samples. So as part of routine care in an intubated, mechanically ventilated baby, the nurses suction out the airway in order to make sure that that endotracheal tube is not blocked.

In general, the nurses just suction out the airway. The suction material just goes into a canister and gets discarded. Well, we save those tracheal aspirate samples. And we obtain those tracheal aspirate samples in conjunction with the routine airway suctioning that the nurses are doing. And we obtain these samples two to four times daily for about two weeks or as long as the baby requires mechanical ventilation.

I should also mention that the babies who are enrolled in the study, their clinical care is dictated by the bedside care team so no baby is kept intubated for any longer than they absolutely need to be. And if a baby gets extubated within 24 to 48 hours of our undergoing the protocol, unfortunately, we lose the data because we need at least five days or so of airway sampling.

From these tracheal aspirate samples, we

can extract the surfactant phospholipid. And then we measure the enrichment of carbon-13 in the surfactant-derived palmitate with mass spectrometry.

This slide depicts a series of approximately 30 babies that we studied. This slide depicts several different issues with respect to the methodology.

Number one, these are the type of data that we obtain from these tracheal aspirate samples. When we extract the surfactant phospholipid from these tracheal aspirates and measure it with mass spectrometry, we can detect the change form baseline of the enrichment of carbon-13 in that palmitate.

So this is a series of babies with -- these are term babies who had normal lungs. These were babies that we studied about five years ago. These were babies who were otherwise in the intensive care unit for some type of problem. And many times these babies had surgical needs or had neurologic injury. And I'll talk a little bit more about that population because it's this population that we propose to study again, a series of pre-term babies with RDS and a series of term babies with respiratory distress as well. These are babies who were studied within the first three to five days after birth.

This is a time enrichment curve that we obtained from measuring the enrichment of the carbon-13 in the palmitate. And you'll notice that the y-axis starts at 18 percent enrichment.

This is the baseline. The tracer infusion occurs in the first 24 hours. And then in the subsequent tracheal aspirate samples, we can gradually see enhanced enrichment of the carbon-13 in the palmitate.

And so with baseline enrichment of approximately 18 percent or the 17.6 percent, we can detect because of the sensitivity of these instruments even just a one to one and a half percent increase over baseline in the amount of carbon-13 in that palmitate.

And so from these data, then, from these curves, then we can do a series of mathematical calculations and come up with an estimate of surfactant synthesis and surfactant turnover. And what we see in these babies, we're looking in this particular case at the fractional catabolic rate or the actual turnover of the surfactant pool.

And what we see in these babies with normal lungs, so, again, these are term babies who require mechanical ventilation for other reasons, the

fractional catabolic rate, or the turnover rate, is 76 percent. So 76 percent of these babies' surfactant pool is turning over in a 24-hour period. So it's relatively rapid, again, alluding to what Dr. Whitsett had referred to.

In contrast, babies with respiratory distress, whether they were pre-term babies or whether they were term babies, had a significantly slower turnover rate. Only 18 percent of their pool was turning over in a 24-hour period, so very, very slow turnover, suggesting some disruption in surfactant metabolism in babies with respiratory distress.

So the main conclusion from that study was that surfactant synthesis was slower in pre-term infants and term newborns with RDS.

Now, as part of our safety monitoring in these studies, we are looking at several different things. But the main concerns or complications that we are worried about and monitoring in these babies are whether there is an electrolyte disturbance during the infusion period or in the 24 hours after the conclusion of the infusion.

This electrolyte disturbance that we're looking for is increase in the sodium concentration and increase in the bicarbonate concentration or a

change in the acid-base balance in the babies.

We are also looking to see whether these babies develop an infection within one month of having undergone the studies. And we're also looking to see whether these babies die within one month after these studies. And these are a very critically ill group.

Our study group was 53 babies who underwent these stable isotope studies. Our comparison group was babies who qualified for our studies, and either we approached the families and they denied consent or, for one reason or another, the baby was not suitable to enroll in the study. So this is a comparison group that is very, very similar in terms of birth weight, gestational age, acuity of illness to the babies who actually underwent the studies.

So when we look at the data from our last four years, we see that there is no difference or about 20 percent of the babies had an electrolyte disturbance, as compared with 42 percent. And these numbers were derived from these comparison babies had we studied them for that period of time, during which we would have studied them had they been enrolled.

So about twice as many babies in our comparison group had electrolyte imbalance. Slightly

more babies in the comparison group had a bloodstream infection within one month of birth and slightly more babies in this comparison group died.

Here are the statistics. So basically what we have concluded from our initial safety data is, number one, we have not identified any significant adverse events during the course or in the period after the infusion. And at this point there does not appear to be any increased risk of electrolyte imbalance, infection, or death from participation in the study.

So that's a little bit of a background. Let's move to the rationale and the protocol for this particular study under question. As Dr. Whitsett alluded to, chronic lung disease or bronchopulmonary dysplasia in premature newborns continues to be a significant cause of morbidity and mortality and is one of the most vexing problems that we deal with in the neonatal intensive care unit today.

We do know from studies from many investigators that certainly the function of the surfactant in babies with chronic lung disease is abnormal, and there are varying studies that suggest that the composition of surfactant to the phospholipid especially and some of the protein component may be

abnormal as well.

As Dr. Whitsett alluded to, nothing is known about surfactant metabolism in premature newborns who develop chronic lung disease. There are animal models. But, again, as Dr. Whitsett pointed out, there is no animal model that mimics the human experience, mimics what we are experiencing in the intensive care unit on a daily basis.

And as a somewhat ancillary note, a study using stable isotopes in pigs found that pigs that were fed diets low in palmitate had lower levels of surfactant to DPPC and decreased lung compliance, suggesting that: number one, palmitate, the availability of palmitate as a substrate for surfactant synthesis, has a direct correlation on surfactant composition and function.

And, as Dr. Whitsett was saying earlier, knowing what we are giving, providing these babies in terms of nutrition, is crucial in order to not only make them grow but ultimately to provide for adequate surfactant composition, synthesis, and function.

So the objective of the study was to determine the rate and contribution to surfactant production from palmitate and acetate in pre-term infants who are less than 28 weeks gestational age at

birth or within the first 3 to 4 days of birth at approximately 2 weeks of age and then again at 4 weeks of age.

The inclusion criteria for the study, first of all, premature infants with respiratory distress who are anticipated to require mechanical ventilation for at least five days. Because of that very slow turnover of the surfactant, we need to have at least five days, preferably seven to ten days of time points after the infusion in order to really adequately assess the clearance.

These babies have to have an intravenous line already in place as part of their routine clinical care. And they also have to be undergoing blood drawing for clinical purposes at least twice a day. Finally, we have to get assent from the clinical care team before we even approach families to participate.

Our exclusion criteria, we have been very, very selective. As I mentioned, I am a neonatologist. I am also very keen to the outcomes from the babies in our intensive care unit. So we are very, very exclusive when it comes to enrolling babies for studies.

So any baby who has a need for escalating

intervention around the time that we're considering their inclusion in the study we don't even approach.

Certainly if death is anticipated, we don't approach the families. If there is evidence of ongoing infection, we exclude the babies. Chromosomal abnormalities or multiple congenital anomalies or any evidence of fluid sensitivity or electrolyte imbalance, those are the exclusion criteria.

Once we have discussed with a clinical care team as to the appropriateness of a particular baby for this study, the frame of mind that the particular family is in, how they have been dealing with having a baby in the neonatal intensive care unit, once we have received determination from the clinical care team that this baby would be appropriate and the family would be appropriate for us to talk with, we talk with the family.

We describe the study in exquisite detail in terms of the use of stable isotopes, that they are nonradioactive, that these are part of naturally occurring substances that the babies are already receiving. And I'll go into more detail in that and what this means exactly in terms of the risks and benefits to the baby.

We then give the family a copy of our

consent form. And we also have a pamphlet that outlines what this study actually means. We give them plenty of time to think about it.

We talk with them again 24 hours later. If they have not decided one way or the other whether they want to participate, we give them more time. So there's no pressure on the families to participate in this study. And so even if they are appearing to be kind of wavering and not really sure, we generally don't pursue it any further. But if the family says that they are interested, then we go ahead and get ready to enroll the baby.

So let me talk a little bit about the tracer preparation because this is one of the key issues of the particular protocol. The acetate and palmitate are commercially prepared as a powder. We use clinical grade or metabolic grade powder that is available from the manufacturers. These are stored under vacuum in a desiccator.

Because the vehicle for these is albumin along with glucose water and albumin is a very good culture medium, we have to prepared these tracers extemporaneously. The standard of care is any albumin solution that's used, cannot hang for longer than 24 hours at a baby's bedside.

So, therefore, because our infusions are 24 hours long, we're operating with a very finite period of time in which we can use these particular tracers.

So the tracer infusates are prepared under sterile fashion by a pharmacologist, a Pharm.D., in our hospital clinical pharmacy in a laminar flow hood. The isotope powder is weighed. It's dissolved in warm glucose water. And then it's filtered through a filter into albumin and the syringe in which that is ultimately going to be taken, labeled, and then taken to the baby's bedside and administered like other infusates for 24 hours. At the conclusion of the infusion, we save it. And then we freeze it for later analysis, if necessary.

Because we have to prepare these tracer infusions extemporaneously, there is really no concurrent means of assessing the tracer. And so we participate and test our preparation procedures very meticulously at regular intervals.

Every three months, we go through the process, prepare an infusate, and then send it to our microbiology lab for routine bacterial, fungal, and viral cultures. We have not had any positive cultures to date.

With each new bottle of isotope that we use, even though they come clinical grade and we have a label that has the sterility and pyrogenicity, we still make up a new preparation, send it off to an analytical lab for particulate matter and pyrogenicity along with a culture. This occurs approximately two to four times a year that we go through this depending on how many studies we do in the course of a year.

And then once a year, just to again test our technique, we do this along with sending the infusate off to a clinical lab so that we can assure ourselves that the constituents that are contained in the infusion are what they think they are so that the amount of acetate is what we think it is, the amount of palmitate and so on.

So it's a pretty extensive preparation procedure that we test extensively in order to ensure that our methods are meticulous and that we are getting what we think we are.

So here are a few details about the infusion. And I have listed the main components of the infusion over here on the left and the amounts of these various components within the infusion and compare them with the usual intake that these babies experience in the course of a day.

So the sodium acetate, the acetate tracer that we use is a sodium salt. Our infusion provides 3.6 millimoles per kilogram per 24 hours in the infusion. The typical intake of one of these babies for sodium is about three to five millimoles per kilogram per day, and acetate is anywhere from one to eight millimoles per kilogram per day, so about the same amount of sodium that a baby ordinarily receives as part of their routine clinical care.

The palmitate tracer that we use is the potassium salt. We use 58 micromoles of palmitate. So it provides 58 micromoles of potassium. The typical daily requirements for a premature newborn are two to four millimoles per kilogram. So we're using about 1,000 times less potassium than is ordinarily required by a premature baby.

Palmitate is part of the standard intralipid or intravenous fat solution that we use, comprises about 7 to 14 percent of the intralipid. And so the amount of palmitate that we're using in these infusions is 58 micromoles. That translates from the intralipid's standpoint to about 1,500 micromoles per day.

So from standard intravenous lipid infusions or fat intake in general in these babies,

they're getting about 30 times the amount of palmitate than we are actually infusing in our tracers.

We use about one gram per kilogram of albumin. These babies receive anywhere from zero to two grams per kilogram per day depending on their clinical condition. And the tracer infusion provides 24 milliliters per kilogram per 24 hours. And the typical needs for a baby are about 100 to 150 milliliters per kilogram per day.

We work with the clinical care team and the pharmacy team to: number one, ensure that we do not disrupt the fluid intake, the electrolyte intake, or nutrient intake of the baby during that 24 hours.

So all of the intravenous solutions are remixed so that they're getting exactly the same amount of electrolytes, calories, and so on during the course of that infusion that they would have received had they not undergone the infusion. And these tracer infusates do not interfere with other intravenous solutions.

So here are the data that prompted us to want to study more babies with normal lungs and, hence, the reason for the discussion of this protocol.

These are a series of babies in which we infused stable isotope-labeled acetate and palmitate

concurrently to premature babies who were less than 28 weeks gestation. The average, the mean gestational age, of these babies at birth was 26 plus or minus 2 weeks.

And these are the results of the tracer infusions, the isotope studies at birth, actually approximately three to four days of age, two weeks of age, and four weeks of age in premature babies who had respiratory distress who continued to require mechanical ventilation at two weeks or four weeks of age. The relative portion of this pathway to the total surfactant synthesis increases.

In contrast, this arm of the surfactant pathway, the unlabeled sources, whether it be from cellular lipids, glucose, fatty acids and so on, or surfactant recycling, decreases in the face of evolving chronic lung disease.

And so then the next question is, are these changes that we are seeing in these babies, these 26-week gestation babies, then at 28 and 30 weeks, a function of development; i.e., is this something that would happen normally to babies who don't have lung disease or is this a function of disease; i.e., these are babies who still require mechanical ventilation, these are not babies who had

respiratory distress at birth but no longer require mechanical ventilation? This is a very select group of babies who required mechanical ventilation for four weeks of age and so have chronic lung disease or are in the developmental phases of chronic lung disease.

So are these changes that we're seeing simply a matter that the baby is maturing or is it the development of chronic lung disease and there is some potential disruption of surfactant metabolism or is it a combination of both? And we don't know the answer to that right now.

We think that the bulk of this unlabeled source of surfactant comes from recycling. We have some animal data from Alan Jobe, who suggested in term rabbits with normal lungs that 90 percent of the surfactant pool in a term newborn rabbit was recycled. In adult rabbits, about 50 percent was recycled. And then in lambs, about 30 to 40 percent was recycled.

We believe that most of this is recycling, although we don't have any data about that as yet, but that then as these babies develop in age or are developing chronic lung disease, that the amount of recycling decreases.

So the hypothesis is that the decrease in surfactant recycling over time is associated with the

evolution of chronic lung disease, rather than normal development in premature infants.

Now, how do we figure this out? And this is the very difficult aspect of this particular protocol. The idea comparison group would be to have a gestational age and chronological age matched set of controls, so babies at 26 weeks, at 28 weeks gestation, and at 30 weeks gestation who have normal lungs.

Well, any baby at 26, 28, or 30 weeks gestation who has normal lungs isn't going to be mechanically ventilated. And, therefore, without an endotracheal tube in place, we don't have access to the airway secretions. We don't have access to the surfactant. So these babies are extremely, extremely rare, babies with normal lungs who require, premature babies at 26 to 30 weeks, mechanical ventilation.

So a more realistic approach is to study babies that have a condition that requires neonatal intensive care with mechanical ventilation, intravascular catheters, and so on, as part of the routine clinical care but who by our best estimates -- and that being looking at gas exchange, looking at chest X-rays -- have normal lungs.

Now, the big caveat is that any baby who

requires mechanical ventilation may not really have normal lungs. However, this is as good as it gets in the real world of neonatal intensive care.

So in general, then, the groups of infants that meet these conditions are generally near-term or term infants who have various surgical conditions. And the most common ones that we deal with are babies with abdominal wall defects because these babies are generally born near term, have normal lungs, but in their postoperative care require sedation and oftentimes require mechanical ventilation in order to get them through the postoperative recovery period.

Sometimes we'll have babies with neurologic defects who cannot breathe because of decreased drive from the central nervous system but who otherwise have normal lungs, babies who have craniofacial abnormalities. And the most common ones we'll see are babies with very, very small jaws who need a tracheostomy placed in order to adequately breathe or babies with congenital heart disease.

And these babies are a little more difficult because many babies with congenital heart disease either don't require mechanical ventilation or their congenital heart disease leads to some disruption in pulmonary blood flow, which can

potentially alter their surfactant metabolism.

So we're dealing with a very, very select group of infants but a group of infants who are critically ill, who require mechanical ventilation, who require intravenous therapy, who require blood drawing as part of their routine care.

This is a chest X-ray of a baby with respiratory distress, as Dr. Whitsett pointed out before. And this is a chest X-ray of a patient, not one that was enrolled in our study, but this is an abdominal wall defect called gastroschisis, in which there was a failure of fusion of the abdominal wall and the intestines flowed out into the amniotic fluid in utero. This is something that's generally picked up prenatally.

So you can see here this is the X-ray of a baby with gastroschisis. And the intestines are protruding out from the abdomen. But the important thing here is that this baby has clear lungs, but this baby also has an endotracheal tube in. So it's on a ventilator.

And this baby also has an umbilical artery catheter, so an intravenous catheter in the aorta to sample blood, monitor blood pressure as part of this baby's routine care. And this is generally the type

of baby that meets the conditions for our studies for the "normal lungs." And, like I said, you can argue whether this baby with all of these accouterments has normal lungs.

So with that in mind, then, the interventions that are specific to this research protocol, then, include the stable isotope infusion -- it's a 24-hour infusion -- and then up to two and a half ml of additional blood that is drawn.

So the risks from this protocol are primarily those from the standard clinical care, blood drawing, airway manipulations, the risk of infection. And the most likely risk for adverse outcome comes from the baby's underlying condition.

The risks that are specific to the research protocol are that it requires two and a half ml of additional blood. We do time the blood sampling to coincide with clinical samples so that the lines are not being broken into more frequently, the baby is not getting stuck any more frequently. We just cluster our needs for blood sampling along with clinically indicated samplings.

The risk from the tracer infusion is infection, but, as we have seen in our experience to date, that risk does not seem to be any greater than

these babies are ordinarily exposed to. And there is that risk of transient electrolyte imbalance, again, that doesn't appear to be any greater from our experience to date.

The potential benefits from this protocol, first of all, there will be no benefit to the subjects themselves. However, we will be able to derive some information about normal -- and I put "normal" in quotes, again, with all the potential caveats for whether these are babies with truly normal lungs, but it will provide us some information about the relative contributions of acetate, palmitate, the other substrate or the metabolic pathways that babies with normal lungs use in order to synthesize surfactant.

Second benefit from this is that these data will provide some context, although not the ideal context, as I mentioned, but some context for interpreting our data from the premature newborns with evolving chronic lung disease.

We might be able to get some idea, is this really a developmental phenomenon. If we find in these term babies with normal lungs that their rate of recycling is only ten percent, then we are going to surmise that what we were finding in the babies with chronic lung disease may be more a developmental

phenomenon, rather than a phenomenon specific to the development of bronchopulmonary dysplasia.

And I think, finally, the most important benefit from these studies is that we're starting to establish new paradigms for thinking about the role of surfactant in newborn lung disease.

And so we are starting to understand that there are some babies -- and I haven't gone into any of these data. Some babies appear to make surfactant just fine. And the chronic babies with chronic lung disease seem to synthesize surfactant fine.

Their metabolic pathways seem to be there. The question is, can they recycle it? Well, it appears that they can't. So maybe it's not a surfactant synthetic problem that they have. Maybe it's a recycling problem. Maybe they're breaking down the surfactant too rapidly.

So we have been so used to thinking that prematurity is a disease of inability for these babies to synthesize surfactant, but some of these studies are suggesting that perhaps that thinking was correct 10-20 years ago, but we're seeing now a subset of babies or a different population of babies whose surfactant metabolism may be disrupted in ways that we hadn't seen previously.

So I think that at the end of when we look at the benefits relative to the risks, that this protocol does provide us the opportunity to understand, prevent, and/or alleviate a serious problem affecting the health or welfare of children.

Thank you.

CHAIRMAN NELSON: Thank you very much for that I think quite illuminating presentation.

I am going to suggest that we take a ten-minute break. And for those of you who have got wristwatches, we'll use that clock as the official clock. So 20 after and then resume our business. Thanks.

(Whereupon, the foregoing matter went off the record at 10:11 a.m. and went back on the record at 10:25 a.m.)

CHAIRMAN NELSON: So as people are finding their seats, the next presentation to basically set the stage for, then, the public hearing and our further discussion and deliberations is Sarah Frankel, who is going to be presenting comments from the reviewing Institutional Review Board at Washington University School of Medicine.

DR. FRANKEL: Thank you very much.

IRB QUESTIONS

DR. FRANKEL: I am very honored to be here. I also want to send regards from Dr. Ludbrook, who is very sorry that he is unable to attend this meeting. He had a rather nasty car accident not too long ago, but, fortunately, he is recovering. He just didn't feel that he was quite up to traveling at this time.

So I am going to be presenting the IRB perspective, a little bit about what we found in the protocol, and then some of the questions that we have that we're hoping you can help us in our deliberations and help us make a determination about.

Okay. So we did find that in the inclusion criteria -- first I guess I should tell you that this protocol was originally approved in 2002. And at that time, it only had the infants with the lung disease. And they were 28 weeks or less at birth. And they were up to six weeks old after birth. And that is something that is recently being added now at the time of renewal.

Something else that is being added at the time of renewal is the controls. And we have found that they are full-term infants with normal lungs that are viable. And they are in the NICU. And they do require mechanical ventilation for breathing

difficulties caused by other illnesses other than lung disease.

We have also found the exclusion criteria are infants for whom death is imminent. So you have your non-viable infants, those with known infections, and those with congenital anomalies and pulmonary hemorrhage.

So the rationale for the inclusion and exclusion criteria would be that the preliminary data indicates the kinetic parameters of surfactant metabolism evolved with infants' age -- and I think both Drs. Hamvas and Whitsett have explained that very nicely -- and to determine the impact of age versus worsening chronic lung disease needed to study the surfactant metabolism in infants without lung disease. And I think Dr. Hamvas explained that very nicely also.

The research procedure is the 24-hour continuous infusion of the non-radioactive stable isotopes acetate and palmitate and the 2.5-milliliter blood draw done in 5 .5-milliliter increments over the first 27 hours, in addition to any routine blood draws.

If there is an in-dwelling catheter, the blood draws will be done through the catheter. If an

in-dwelling catheter does not exist, there will be two to three blood draws done at clinically indicated times.

Then the clinical procedures used will be the tracheal aspirates that are going to be obtained with routine airway suctioning over the next 14 days as long as the infant is intubated and blood samples that could be drawn before the infusion begins at selected intervals over the next 2 weeks after the infant is enrolled. And the amount of blood is doing to be dependent on the treatment for the illness.

So we found that the research risks were a rare risk of bloodstream infection. We do understand that the isotope infusions are prepared in sterile fashion by the pharmacists and that the rate of bloodstream infection will be monitored by the data monitoring committee. And the clinical risks would be the need for blood transfusion that usually comes about because of the infants' illness, not because of the research.

We do agree that there is a benefit to better understand how surfactant is made and used in premature infants. So we do feel that this information from this study could help us understand surfactant production and could potentially provide

information that could help alleviate or prevent lung disease in infants in the future. But at this time, there are no direct benefits to the infants.

We looked at category 2 under expedited procedures for blood draw samples. And we found that category 2 does not include or exclude the collections through a catheter. And it does specify two times per week for the collections but through the finger stick, heel stick, ear stick, or venipuncture.

So one of the questions would be, can more collections be done if you're using a catheter? And then would the study qualify as minimal risk?

Then in looking at the risk categories for minors, we find that it doesn't fit minimal risk or 46.404 because of the 5 blood draws done in the 27-hour period; that is, barring my previous question. Does that still hold true if you are using a catheter and the rare risk of bloodstream infections?

We also find that it doesn't fit 46.405 because there is no direct benefit to the participants. In looking at 46.406, we have now added a control group in the NICU that has illnesses that are not related to lung disease.

So even those control group is other than healthy. They don't have the disease being studied.

So information would be generalizable but not to the specific disease that you have. If you're looking long-term, could potentially these participants benefit?

I think Dr. Hamvas did a nice job of explaining that potentially in the future they could, but at this time they would not. And also the control group would not necessarily have stable isotopes infused, nor would they have the additional blood draws done as part of their routine care.

In looking at 46.407, we have a control group now that is considered healthy, but they're not really healthy. And then we have the infusion of isotopes and the five blood draws.

So we felt overall that even though the control group is not really healthy and that indirectly information could be obtained that could help this control group in the future as we find out what is happening with surfactant production and how that leads or does not lead to potential lung disease, but that it doesn't really fit the spirit of 46.406.

So we thought it was best to refer it to this Committee so that you could help us make a determination. In the past, when it was only the infected group, we did approve this protocol under

46.406.

CHAIRMAN NELSON: Thank you.

We have now a half an hour before our scheduled open public hearing. So my suggestion is that we use that time to ask questions of either Dr. Hamvas or Dr. Frankel about the protocol or IRB process. So we'll just open it up to panel members and start with Joan and then Roan.

DR. CHESNEY: I have some questions for Dr. Hamvas. As a non-neonatologist, I just wanted to be sure that I really understand the purpose of the study. And my first question actually has to do with the slide incorporation of carbon-13 acetate into surfactant, which has been published in Pediatric Research.

And you used there some normal infants. How many did you have? And do you have reason to believe that -- are you just looking for an additional population or to increase your numbers or do you have any reason to question that result?

DR. HAMVAS: So in that original group, there were seven term infants with normal lungs by the criteria that we have used. We used the single tracer, carbon-13 acetate. And so that and we trust those data implicitly.

What we found out with our subsequent studies with the premature infants, though, when we used both tracers, both the acetate and the palmitate, is that at each age of the premature infants that we studied, the palmitate provided a greater contribution to the overall surfactant synthesis than did the acetate.

And so, in essence, what we were looking at in those previous infants with normal lungs was actually one of the minor pathways of surfactant synthesis. And so that prompted the subsequent questions, not only the questions I address but if we're only interrogating the minor pathway but, yet, palmitate is providing the more predominant substrate for surfactant synthesis, are we missing a significant proportion of surfactant synthesis in this term population with relatively normal lungs? And so that was a side impetus for wanting to study the additional babies.

DR. CHESNEY: Thank you for clarifying that.

My second question -- and forgive me if I don't express this as well as you have -- the major issue is the metabolism or turnover of surfactant in infants who go on to develop chronic lung disease and

that their recycling rate is only ten percent. And your concern is primarily with the surfactant turnover that isn't tracer-labeled. Am I expressing that well?

It's your slide labeled "New surfactant synthesis in ventilated pre-term infant newborns." And you pointed out that with increasing age, more of the surfactant had the tracer label in it and that meant that less of the surfactant being synthesized through other pathways.

And is the theory correct that you're concerned that there is less being produced by other pathways and that may be because of increased metabolism or decreased synthesis?

DR. HAMVAS: Right. So I think there are several questions that have come about from those observations. Number one, when we're doing these tracer studies, this is going to be a very difficult concept to try to put out. So what we're looking at with these tracer studies is the relative proportion of these various metabolic pathways and the relative proportion of surfactant turnover.

So we have found from these tracer studies that depending on the age, 50 percent, 70 percent, 90 percent of the surfactant pool is turning over per day.

Now, that's one part of the equation. The other part of the equation is, what is the size of that surfactant pool? Is the surfactant pool large enough to provide adequate lung function? We don't know the answer to that question, number one. And, number two, we don't have any immediate ways of testing that, although we're in the process of developing some of those.

But what we can say is that there appears to be a decrease in contribution from these unlabeled sources of surfactant, just like you said. And so if that bulk of that is due to recycling, it appears that these babies can synthesize surfactant, at least from the acetate and palmitate pathways.

But what we don't know is are they making enough, for one thing? And, secondly, if they are unable to recycle it, is that recycling a critical component of maintaining surfactant pool and surfactant function or is it something that happens in the normal development of surfactant synthesis in the otherwise healthy lung?

DR. CHESNEY: Thank you.

CHAIRMAN NELSON: If we're going to Ron, let me just ask one clarification. These samples at zero, two, and four weeks, were they paired or

unpaired? Were these different premature points in time? And if they were the same, how would you rule out build-up of the isotopes within the overall pool?

DR. HAMVAS: So some of the babies were the same. There were maybe out of that whole group two babies whom we had time points, all three time points.

Most of the babies were just babies who were studied just an individual time, either at two weeks or for plus or minus a week or so. We don't believe that that's build-up because if you go back to the slide that shows the turnover from our 2003 Pediatric Research publication, the tracer is essentially out of the system by about 10 to 14 days of age.

So what we're seeing, the tracer has essentially been washed out by the time we do the second infusion. So that's issue number one.

Issue number two is, before the start of the infusion, we always get a baseline sample so that we have background enrichment. And then everything that we get subsequently is compared to that background enrichment at the baseline sample.

CHAIRMAN NELSON: Ron? And then Mary Faith.

DR. RUBENSTEIN: I have a few questions. The first one relates to you mentioning that five years ago you studied with similar methods a similar non-premature group.

DR. HAMVAS: That's correct.

DR. RUBENSTEIN: Okay. So for me, what is the significant differences between these two protocols that would alter the risk/benefit analysis? And also you may or may not remember and maybe Dr. Frankel knows, but under what part of Subpart D was the previous protocol approved? I feel fairly comfortable that it did not go to a 407 panel.

DR. HAMVAS: It did not go to a 407 panel. I believe it was under the 406 originally.

DR. FRANKEL: Yes, it was under 406.

DR. RUBENSTEIN: The non-premature infants were approved under 406.

DR. HAMVAS: Right. And from my way of thinking, I'm not sure that what we're doing with this particular protocol is significantly different from what we did three years or four years ago.

DR. RUBENSTEIN: Okay. So it's basically the same preparation of infusion, similar constituents to make up the infusion, similar sampling, so on and so forth?

DR. HAMVAS: Right. The only difference is that with using the palmitate, we have to use albumin to bind the palmitate. So the difference is the use of albumin in the infusion.

DR. RUBENSTEIN: Okay. Second question is that you stated you've done many of these infusion preps without any evidence of contamination, infection, and so forth. Can you hang a number on that?

DR. HAMVAS: Well, I guess I don't have a specific number. Basically all we have is our comparison studies looking at population of babies who would otherwise qualify for the study but were not infused and that we do not appear to have any higher rate of infection in the babies that we have studied.

DR. RUBENSTEIN: Next question.

DR. HAMVAS: Maybe I should mention, too, that every time we have gone through our tracer preparation and actually tested our preparation, our cultures have been negative as well.

DR. RUBENSTEIN: Do you have a number about how many times that has been?

DR. HAMVAS: We do it about three times a year or four times a year, every three months. So 40-50 times.

DR. RUBENSTEIN: Okay. The IRB-approved consent form for the premature infants states that infection is expected to be a rare or very rare complication. What does that mean at Wash. U.?

DR. HAMVAS: Well, the --

DR. RUBENSTEIN: Maybe Dr. Frankel can help you out. What do you guys mean when you say it's expected to be an extremely rare complication?

DR. FRANKEL: We actually have an assessing risk guideline. And one of the criteria that -- or information that the reviewers can use comes from the NCI. And rare is less than two percent. That's if we have percentages for the protocols. So we use that as a rough guideline.

So when we're talking about something that is rare at Wash. U., we're talking about something that is pretty rare.

DR. RUBENSTEIN: Okay. If you were to write future directions for this research as to how it would ultimately be applied to patients, what would you say?

DR. HAMVAS: Well, I think one issue is looking in more depth at the nutritional components of the substrates that we're providing to these babies in order to maximize surfactant synthesis. That's number

one.

Number two is to interrogate that recycling aspect. And there are theoretical ways that we can do that by using a labeled airway tracer and assessing surfactant recycling. So those would be the two major components.

What that could potentially lead to therapeutically for children is, number one, might alter the nutritional composition that we provide to sick premature infants. We have already found that palmitate seems to be the predominant precursor should we be providing them more palmitate than we actually are in our current nutritional solutions. I realize that's a very narrow viewpoint.

DR. RUBENSTEIN: Do you think there is insufficient evidence to do that at the present time?

DR. HAMVAS: I don't think we have evidence one way or the other to do that. Secondly, I think that if recycling or catabolism is an issue, if we're finding that babies are breaking down the sort of catabolizing surfactant more rapidly, should we be looking at surfactant preparations that are actually more stable and less susceptible to catabolism so that we can maintain that alveolar pool size?

DR. RUBENSTEIN: And one last sort of

question and comment. I wonder if the comparison group -- and I'm using that word as opposed to a normal control group -- should be more properly called a disease control group? Because then I think you have a better, and sort of an editorial comment, chance of understanding this under 406 because most people I think would agree that people on ventilators have some alteration in surfactant, even though it's probably the best you can do.

And I agree with that. I am not sure that they have normal surfactant metabolism.

DR. HAMVAS: Yes. That's an excellent point, yes.

DR. RUBENSTEIN: Thank you.

CHAIRMAN NELSON: Mary Faith? And then Mark.

DR. MARSHALL: I have a couple of questions. One is about your data monitoring plan, which is very nicely done and outlined.

But my question is this. You say that the data that you are compiling about your research participants will be compared against otherwise eligible infants who were not studied. So how do you accrue those data? From whence do they come?

DR. HAMVAS: Well, we actually do accrue

the data by looking at the babies who were eligible. And then if the parents decline consent or if the baby is not studied, for one reason or another, we collect that data, the clinical data, just the infection, the electrolyte imbalance, and the survival data.

DR. MARSHALL: Are those identifiable data?

DR. HAMVAS: No.

DR. MARSHALL: Okay.

DR. HAMVAS: I mean, they're identifiable from the standpoint that we know which babies we have approached and so on, but once we have completed our monitoring, there are no identifiers.

DR. MARSHALL: Okay. Thank you.

My second question has to do with your previous control group and your data that were reviewed on the 4th of October of last year. It looks as though your previous sort of control group was also pre-term infants and that if you look at the data, that the mortality rate among that group was actually higher than among the group that you studied in terms of outcome.

I'm not making a critique. I'm just trying to get a sense in terms of the proposed control group, that would you expect the morbidity and the

mortality rates to be similar between the two groups or could you give me just a sense of what you might anticipate there?

DR. HAMVAS: Yes. So I'm not sure I'm following which control group here.

DR. MARSHALL: Okay. So I'm looking here. So these are your data and safety monitoring plan, data reviewed October of '04.

DR. HAMVAS: Okay.

DR. MARSHALL: And it says that of your 18 subjects in this study, you had one death, not you but one of the subjects died. And of the eight control patients, two died. So it seems as though that the mortality and their morbidity would be expected to be at least similar between the two groups. That's all I'm asking. I'm not --

DR. HAMVAS: Okay. And so to try to clarify, number one, the control group there, the use of the word "control," is generally pre-term babies who were otherwise eligible for the study --

DR. MARSHALL: Right.

DR. HAMVAS: -- and that were not studied, --

DR. MARSHALL: Right.

DR. HAMVAS: -- in contrast to the term

"control" that we have been using for the healthy or the --

DR. MARSHALL: Right.

DR. HAMVAS: -- babies with normal lungs.

DR. MARSHALL: Normal lungs, yes.

DR. HAMVAS: Right. So one of that, yes, you would expect fairly similar. But, again, some of the babies in that comparison group we excluded. The families did actually consent for the study.

And I think out of that 57, there were about 8 or 10. I don't remember the exact number who consented to undergo the study but a change in the baby's clinical condition caused us to step back and say, "We're not going to study."

So, you know, there is a small group of babies in there who were not studied because of change in their clinical condition, which could contribute to the higher.

DR. MARSHALL: Okay. Thank you.

And this question, Dr. Frankel, this is kind of for both of you. And it's relative to the consent document, I guess to not really questions perhaps but points that I would want to make about the consent document. And that is under the question "What are the risk?"

Sort of the first thing you see there is research-related, likely "none." And I'm speaking for myself here, but there are always either unanticipated risks that attend to studies, there is human error.

So the word "none" I find hugely troublesome to ever find in a consent document for research, especially biomedical research. So I'm making up that point. And I'd even go so far as to say -- I'm not speaking for OHRP, but if I were on a site visit with OHRP, I'd find that really bothersome.

And the second thing is under the "Alternatives" sections, under the "Benefits," it seems to imply what the alternatives are for the researchers, as opposed to the subjects, because it says there are no alternatives, there are no other alternatives, for studying surfactant metabolism in babies.

The point of this is, what are the alternatives for the research participants? And always 100 percent of the time, an alternative should be not participating in the study. And that should be outlined there under the alternative section, even if it's mentioned later.

So those are two observations that I would make that are probably relatively minor but wouldn't

be for me if I were paying a call on your place.

DR. FRANKEL: I could actually comment to both of those. So yes, what should we do? Ask that the researchers outline the risks as likely, less likely, and rare, but if they don't feel like that there are any risks that fit into one of the categories, we usually ask them to sort of remove that. I know this was approved with "none" on there, but quite frequently we'll catch that and ask them to just remove that so it doesn't say "none."

And there was a version of our consent -- and this is one of them -- where we actually did talk about the study being voluntary and that individuals didn't have to participate.

We had actually moved that to section 7. And then when they asked us to move it back to section 6 so it was more obvious, one of the things that we had tried to do with our consent is to increase the readability. And in doing that, we try to be a little less verbose. Maybe it wasn't as obvious then.

And so in our current version, it's actually back under "Alternatives." And it's --

DR. MARSHALL: Good. I'm glad. I'm glad to hear that. Thank you very much.

CHAIRMAN NELSON: Let me go to Mark. And

then I'll go down to Jill, Paula, and Angela.

DR. HUDAK: I have just a few unrelated questions that I just need to clarify. With respect to the protocol itself, the consent is obtained at what point? Is it shortly after birth? Is that when it's obtained?

DR. HAMVAS: It depends on the baby being studied. So if it's one of the babies who is being studied in those first few days after birth, we will generally look at the baby for 24 to 48 hours once there is a little bit better idea of what the kinetics of the baby's illness are, then start the consent process. So it's usually after about 48 hours that we first talked to the family.

The babies who are studied at 2 weeks or 4 weeks, we've determined that they were potentially candidates in the newborn period, but for one reason or another, didn't approach the family, revisit them at about 10-12 days of age and at that point, if they're appropriate, then approach the families. And then the same goes for the babies who are at four weeks.

So the approach for consent is about the same time point as within 48 hours or so of doing the study. When we first approach parents, even in that

early time point, we say "We may be approaching you again in two weeks or four weeks if your baby is still potentially eligible." And if the baby is still eligible, we will re-consent them at that time, at the later time point.

So every study that we perform has gone through the consent process. So some of these families, a couple of the families, actually went through three different consent processes.

DR. HUDAK: That answers my second question. With respect to the infusate, you had presented the information on the composition. For the very pre-term infant who is getting this, this is a significant sodium and fluid load. Do you make allowances in your clinical care during the day to take that into account?

DR. HAMVAS: Right. I mentioned that we adjust the other infusate so that basically if that baby has required about 3 to 4 milliequivalents per kilogram in that 24 hours, the only sodium that they will receive will then be through that infusion. So we adjust all the other fluid, the composition of the fluid, so that nothing is changed that the baby is getting, just their appropriate need.

Now, if a baby is eligible and we see that

their sodium is 155 at the time of the study, then we don't study them.

DR. HUDAK: Okay. The babies that you have studied obviously are a population of babies who are ventilated for which you think that they're anticipated to be ventilated for another five days. That's --

DR. HAMVAS: You know as well as I do that you can never predict, right.

DR. HUDAK: You certainly can't. And there is a whole other group of babies now who are extubated very aggressively. And, again, it's unpredictable whether it's going to succeed or not in the long term, but there are quite a few small babies now who come off the ventilators who do very well.

And so I have a very hard time with any given baby saying whether this baby is going to need ventilation for five days or not or live or die or whatever. It's just not predictable.

But I think the point is that clearly there is something different about the baby who continues to require ventilation versus one who doesn't. And it's unknowable exactly what you would find if you were able to get the same data for that population of babies at the same postnatal age and the

same gestational age, which is a long way of my getting around to the second point of the control group you've outlined: the babies who don't have lung disease who have got the abdominal wall defects, neurological defects, congenital heart, craniofacial sort of things. Most of those babies are more toward the term.

I guess the question is whether or not -- I'm trying to put in my mind exactly what that information is going to tell you because the population you're looking at -- and that population is very different. Things may be different between the two on the basis of gestational age, may be different -- as you point out, may not be actually control lungs or normal lungs. And so you're going to get some information there.

Could you sketch out exactly what the real contributions, taking a range of information that you might find out about that population will contribute to future interventional studies?

DR. HAMVAS: Sure. Yes, you bring up some very, very important questions and difficult questions that we have been wrestling with since we have been doing these studies. And it all comes down to we need airway access. And we're not going to get the

information if we don't have airway access.

So yes. Admittedly, these near-term/term babies are a significantly different population than that population of babies we are actually getting data from.

I think that the information that we will get from these near-term babies, I think, number one, we will see what the relative contributions of palmitate and acetate are to surfactant synthesis.

Now, we will have an idea of what the turnover rate and the relative contributions of those couple of pathways to surfactant synthesis are in the near-term/term babies. If they are more or less the same as what we see in the premature babies, then we can speculate, although we're not going to be able to say with absolute certainty, that perhaps what we're witnessing is just a developmental phenomenon in terms of the evolution of surfactant metabolism in babies.

If they are significantly different, however, and if the term babies or this "disease" comparison group are anywhere similar to what Alan Jobe's animal studies have suggested, suggests that about 90 percent of the surfactant pool is recycled in a 24-hour period in the term rabbit.

And if we find that that is the case in

these term newborns, then we're going to make the assumption again. It's not going to be with absolute certainty that something is happening that's decreasing the amount of recycling as these babies are developing chronic lung disease. And it would suggest to us, then, that there is an issue with recycling in these particular babies.

Now, again, there is the whole issue of surfactant pool size as well. You know, do the term babies have a normal surfactant pool size and pre-term babies have an abnormal surfactant pool size or a normal? We're not going to get at that question with these particular studies.

I think it will provide us at least some reference point from a developmental standpoint as to what surfactant metabolism should look like in the near-term or term baby with normal gas exchange and perhaps then give us some intuition about what is happening in these babies at 30 weeks. I don't know if I answered your question satisfactorily or not.

DR. HUDAK: It helps.

CHAIRMAN NELSON: Thanks, Mark.

Before turning to additional questions, we have reached the official time for our open public hearing. Let me just ask. I know Dr. Whitsett has

indicated a desire to speak as part of that hearing. Are there other people here that have asked for that opportunity?

(No response.)

CHAIRMAN NELSON: Then I have a question for Dr. Whitsett. Is it all right with you if we continue the current line of questioning and at some point in the next half-hour, we get to your comments? Is that fine?

DR. WHITSETT: Anytime.

CHAIRMAN NELSON: So why don't we continue with our line of questioning, and then we'll do the public hearing. Jill? And then, Kate, did you put up your hand? So we'll go Jill, Paula, Angela, Kate. It looks like everybody. All right. I'll write them all down. Thank you. Go ahead, Jill.

MS. FISCH: Well, having been the parents of a critically ill child in the NQ two weeks on a ventilator sitting by his bedside, what I'm wondering is, how are the parents approached? And do you give them access to a social worker for their questions?

In reading the informed consent, I see they can call Dr. Spence, they can call another physician, they can call a privacy officer, but I don't see them having any access to somebody else who

might be able to answer their questions and may not be as intimidating as speaking to a physician who wants their child to participate in a research study.

Another thing that concerns me looking at the informed consent, what we have to realize is a significant portion or a decent portion of the population reads on an elementary school reading level. And I find, you know, while I certainly understand this, that things could be better explained, that there are things in there that are not clear.

And it may lead to people wanting to ask questions and being uncomfortable asking them. And how do you handle it at the hospital? Do you have a social worker who is working with you on this for the families?

DR. HAMVAS: Well, we don't have a social worker per se, but I would say that the biggest filter that we have is the bedside nurses. And so the nurses in our intensive care unit understand that the neonatal ICU at St. Louis Children's Hospital is one in which there are opportunities to participate in research studies.

Among the many different studies that are going on in our intensive care unit, we have regular

sessions with the nursing staff that outlines the various studies that are going on. So that the nurses are versed at least in terms of who is performing which study.

The families feel very comfortable talking with their bedside nurse, as you know --

MS. FISCH: I know.

DR. HAMVAS: -- about all aspects of the baby's care. And so we have found that our nurses are able to -- at least if they can't answer the question specifically, we always leave a note at the bedside to say we would like to approach this family for a stable isotope study if they have questions and then leave Dr. Spence's or my pager number at the bedside so that the nurses, the bedside nurse, can call us any time of the day or night.

And we make it very, very clear that these studies are very complex. They're very important. But, yet, we don't want to interfere with the normal care, the routine care of the baby, and we don't want to disrupt that very fragile family dynamic that occurs in the course of the intensive care.

So, therefore, when we're talking about approaching these families, we involve the bedside nurse in those discussions as to whether this is a

family that is appropriate to approach.

We also make it very clear to them that we don't mind being called at 2:00 o'clock or 3:00 o'clock in the morning with these questions when the parents are at the bedside and just come up with them because we would much rather have a question get answered and so that the family does have that information and then can make an informed decision one way or the other.

So that is kind of a long-winded answer to your question, but we use the nurses a great deal as our way --

MS. FISCH: Is that something that could be added to the consent, that the nurses are available to speak with for questions as well as the physicians who are conducting the study, so that people know?

I mean, even though you're sitting there and you're talking to the nurse, there's so much going on and you have so many questions about the care of the child itself with whatever the child is in there for in addition to this. And I think it's just a lot for parents to handle.

Reading this, maybe somebody wouldn't think to ask a nurse a question. And maybe if they see it in writing and they say, "Oh, then I have

access to ask the nurse what I would like to ask" and the nurse can approach the doctor and that may make families feel more comfortable --

DR. HAMVAS: That's an excellent point, yes. Thanks.

CHAIRMAN NELSON: Thanks, Jill.

I'm going to make a suggestion. What I would like to do is just sort of move around. And if we could focus on questions, we'll have three hours this afternoon to sort of do our own deliberations as well. And I'm just concerned that in the next half-hour we sort of get through what is now a fair number of individuals that would like to ask some questions.

MS. FISCH: I'm done.

CHAIRMAN NELSON: What I'm going to just do is go around and let's sort of focus. And if you don't have a question, just say, "No question." Kate?

MS. SHAFER: I had a question about the blood drawing that is described in both the pre-term infants as well as the comparison group. It says that 5 samples of one-tenth of a teaspoon each would be drawn over 27 hours when there is an in-dwelling catheter or when there is not an in-dwelling catheter, there would be 2 or 3 samples taken during other

routine clinical care time frames.

A couple of questions related to that. Is that the same amount of blood that's drawn over the 5 blood samples over 27 hours compared to 2 or 3 times?

DR. HAMVAS: No. It's 0.5 ml --

MS. SHAFER: Per?

DR. HAMVAS: -- per sample regardless.

MS. SHAFER: Okay. And, then, does that yield the same kind of information? Can you compare two blood draws with five blood draws over a longer period of time?

DR. HAMVAS: Well, we can depending on when the samples are obtained. Ideally we use the blood sampling to assess the level of the isotope in the bloodstream.

So ideally we would like to get one just before the start of the infusion at three time points during the infusion to assure that we have what we call steady state, that the amount of tracer is flat and then at the end of the infusion or within two or three hours after the end of the infusion, to see that it has died away.

We can get by with two samples if we can obtain it right before the infusion and then one sometime during the infusion, but what we lose there

is that we're seeing that we don't always have the ideal curve. It's not always the same amount at every step.

So we potentially lose information by not having the additional blood samples within the time frame of the infusion.

MS. SHAFER: So if you are losing information, is there a reason that you would not only enroll babies who are going to have an in-dwelling catheter over the time period that you need, rather than having them be stuck, granted for other types of care, but you may not have data that would be very useful to you?

DR. HAMVAS: Yes. That works in the babies shortly after birth because they generally have an arterial catheter, from which blood is drawn. By the time they are two weeks or four weeks out, those kinds of catheters have generally been removed. And so we don't have access to the routine frequent blood sampling in those later ages than we do at the early ones.

So then that distills the population even further in terms of the population of babies that we are studying at four weeks. If they still have a new arterial catheter and this is a select group of babies

who is extremely ill and is felt on the part of the clinical care team to require that frequent blood monitoring, which is a significantly more distilled population than we were looking at beforehand.

So, again, we're making compromises at every step along the way, trying to achieve the best information that we possibly can. And so by the time we're getting out to the babies at four weeks, they're generally having blood sampling only twice a day. And we understand that we're potentially losing information or could potentially get erroneous information as well.

And we can tell if we're getting very erroneous information if the sampling point seems to be just way out of proportion to what we have seen before. We may end up discarding that data altogether.

CHAIRMAN NELSON: Paula?

MS. KNUDSON: Well, I, too, have been concerned about the consent process with these babies and families. Not only do I think of the babies as being highly vulnerable and very sick, but I think with parents as being highly vulnerable.

I am very concerned about the concept of the therapeutic misconception. Do these parents

really seem to understand that their very sick baby is really not going to directly benefit from these studies?

DR. HAMVAS: Well, we're very clear when we talk to the families that we will not get any information that will help their baby. As a matter of fact, we're up front with them that tells them that the results of this study, we may not know the results of this particular study for several months after it has been performed.

So we are very, very clear that the baby will not benefit from the study, that what this will provide is potentially the opportunity to help not any of the other babies that are in the intensive care unit right now but other babies down the road who may be in a similar situation.

MS. KNUDSON: Thank you.

DR. HAMVAS: We're also very sensitive to that vulnerable aspect of the families, too. And, like I said, I'm a neonatologist, first and foremost. And so, like I said, if we get a lot of babies who are transported in from some distance, we do not study the babies.

We do not get consent over the phone. We want to meet the families firsthand. We get an idea

of what the families' psyche is around the time. And our nurses are very, very good at helping us understand what that is. So we are very, very sensitive to those issues.

CHAIRMAN NELSON: Angela?

MS. HOLDER: Yes. I don't really have a question, but I think the consent forms in general need to be seriously rewritten at a much lower level of comprehension.

And I specifically agree with Mary Faith that you never put "None" of consents. Question 7, particularly about HIPAA, is very confusing. And there's actually one mistake, which is HIPAA has nothing to do with sharing information with primary care physicians who are taking care of the patient.

And I think that, in particular, but the whole thing strikes me as extraordinarily complicated just in terms of anguish and grammar and the way it's put together.

CHAIRMAN NELSON: Thank you. "HIPAA" is HIPAA for those who don't -- Mary Faith? Nothing. Ron?

DR. RUBENSTEIN: No.

CHAIRMAN NELSON: Alan?

DR. FLEISCHMAN: I really appreciate your

presentation. And I think we have learned a great deal. I want to focus on the near-term group because I think that's why we're here at a 407 discussion.

And what I didn't pick up -- and maybe the number of eligibles per year that exist in your neonatal unit or somewhere in the institution of those infants, and then I have a question after that.

DR. HAMVAS: Okay. I don't have a specific number. I can try to construct something. We get about 20 or so abdominal wall defects a year. We'll probably get 10 to 15 babies with central nervous system disturbances, although we generally shy away from those given the extenuating circumstances of those, maybe one of the craniofacial abnormalities

So in general, our population is probably about -- you know, the baseline population is 20 to 25. Of those who require mechanical ventilation for the determined period of time and so on, it's significantly less than that. I don't have a clear number, but I would guess when it comes right down to it, we maybe have at most ten eligible infants a year.

DR. FLEISCHMAN: The second question has to do with power. In your power analysis, you talk about groups and needs for a minimum of ten. I think that's both optimistic in terms of number and perhaps

less than you're going to need because of the variation in this group that really isn't normal or may not be as normal as we'd like to think.

So in terms of the power here, do we really think that we will within a reasonable time frame of the life expectancy of Dr. Spence and the research, you know, in terms of her research career, will that happen? And then I have a third question.

DR. HAMVAS: Yes. Well, we have gone around and around with the power analysis. The power analysis, we looked at a 50 percent difference in the rate of total surfactant production as our delineation points or demarcation points and found that 10 infants from this comparison group should be sufficient to provide that 80 to 90 percent power.

And we were anticipating over about a two to three-year period of time to be able to accrue these. With our previous seven babies, it took us about two years to enroll those seven babies. So we were kind of looking at similar types of time frames.

DR. FLEISCHMAN: Here's the hard question. If we gave you infinite money and a non-human primate colony, wouldn't you be better off doing those studies in that environment where you wouldn't have chronic intubation, you would have normal lungs and you'd

learn a heck of a lot in an animal model that I think is pretty comparable to the full-term newborn human?

DR. HAMVAS: Yes. Even if we used animals, a premature baboon --

DR. FLEISCHMAN: Not premature. It's the term that I'm talking about.

DR. HAMVAS: Oh, oh. I see.

DR. FLEISCHMAN: You see, Dr. Whitsett is right. We have not succeeded in having monkey neonatal intensive care units, although we could, and we did a little bit of that back 30 years. But what about the term monkey?

DR. HAMVAS: Well, that's a good question. We have talked about perhaps doing animal studies. The question that we really don't know is how similar are the baboons to term newborns under these kinds of conditions.

Certainly, I guess, given infinite amounts of money and ability to perform these studies, that would certainly be one reasonable possibility.

CHAIRMAN NELSON: Mark?

DR. HUDAK: I'll pass but reserve the right to come back.

(Laughter.)

CHAIRMAN NELSON: You have that right.

Joan?

DR. CHESNEY: I have several hopefully very short questions. Apparently your IRB was concerned about the infection risk in the normal population. And the blood draws are happening anyway. So I assume their concern about the risk had to do with the 24-hour hanging of the albumin tracer preparation and the risk of that becoming infected.

I wondered if you had done any cultures at the end of your infusions of those bags and demonstrated that they were always sterile. I didn't know if that could help your case in that sense.

DR. HAMVAS: That's a good point. We have not done that. And part of the reason for that is if we came up with something, I'm not sure I'd know what to do with the information.

DR. CHESNEY: Well, I agree.

DR. HAMVAS: Certainly, we would have to approach the family and talk with them. But it's a difficult situation, yes. We have not done that.

DR. CHESNEY: Well, I agree. And even as an infectious disease person, -- many Dianne knows -- I don't really know what the risks of hanging albumin for 24 hours are in terms of infection. But that seemed to be the main issue that they were concerned

about.

DR. HAMVAS: And it's something that we do as part of our routine clinical care as it is. Many of our babies have albumin mixed in with their parenteral nutrition solutions. So it's part of standard care.

DR. CHESNEY: And you hang them for 24 hours?

DR. HAMVAS: Right.

DR. CHESNEY: I wondered if you had picked up any differences between the infants that you studied that were extubated after two weeks; in other words, they didn't fall into that chronic lung disease group, and those that were still intubated after four weeks.

In other words, do you see improved recycling of that unlabeled pool in those infants that don't go on to be intubated for four weeks? Does it make sense?

DR. HAMVAS: Yes. That's a good question. Yes. We actually did look at that. And we didn't see a difference, but, then, part of that is potentially a power issue as well because at the 2-week time point, we had -- I'm trying to remember -- I think it was, 9 babies altogether and then at the

4-week time point had 16 babies.

So we did look at that. We didn't see a statistically significant difference, but whether that's a biological phenomenon or a power phenomenon, we don't have enough information.

DR. CHESNEY: My last question is probably going to sound very ignorant, but please understand I was a chemistry major if it sounds hopelessly ignorant. But why are you drawing blood? What do you do with the serum concentrations of tracers because most of your data is based I think on the levels in the lungs. Do you do some kind of proportion? And do you see changes in the serum concentrations?

DR. HAMVAS: So the reason we're drawing the blood is in order to calculate one of the parameters that I didn't address -- it's called the fractional synthetic rate -- we're looking at the relative amount of the tracer in the tracheal aspirate surfactant and comparing it to the precursor enrichment so that we get an idea of what the flux from the bloodstream into the surfactant is.

And so the reason for the blood sampling is to get an understanding of what that enrichment is. And then we can adequately interpret what we're seeing after the incorporation into the surfactant.

DR. CHESNEY: So you do it relative to the surfactant. Can those numbers alone tell you anything?

DR. HAMVAS: Generally not. It tells us how much -- what the enrichment of the tracer is in the plasma, but that in and of itself, we do see from baseline to the infusion a slight increase in the precursor enrichment or the plasma enrichment.

But those numbers in and of themselves right now, we could potentially use that information for other aspects, looking at other aspects of nutrition and fat handling and so on in newborns. We have not done that at this point. We have just focused on the surfactant aspect.

DR. CHESNEY: I had one last question. Do you ever, do neonatologists ever, use surfactant after the first 48 hours; in other words, an infant who you think is becoming a chronic lung disease patient? And if in your hypothesis maybe that there's not enough surfactant pool because you have increased recycling, have neonatologists ever given surfactant after a month to see if it makes a difference?

DR. HAMVAS: So I'm talking at the FDA.

DR. RUBENSTEIN: I may be able to help you out with that. There actually is a trial going on now

where they are looking at surfactant weekly. And I think I can say that at the FDA because I know the FDA knows about it.

DR. HAMVAS: Right, right. And we're participating in that study with the investigators.

DR. RUBENSTEIN: Yes.

DR. HAMVAS: So yes, it is something that is being tried on an investigational basis right now to determine if later surfactant administration does alter the outcome. We are in the process of participating in that study. And at our center, we are in the process, then, of we would like to do these stable isotope studies in those particular patients so we can see whether that additional surfactant alters surfactant metabolism and whether there may be additional benefits beyond just simply administering the surfactant.

DR. CHESNEY: Thank you.

CHAIRMAN NELSON: Michael?

DR. FANT: Yes. As a neonatologist, I would like to just comment on what I think is the importance of this line of investigation to helping us understand the dynamic and complex nature of surfactant deficiency in premature lung disease and trying to better be able to deal with it.

And having said that, I'm going to come back to what may be a hard question. And that's back to the control group. You mentioned in your presentation that in terms of the surfactant production that you see, the various components that contribute to the production vary over time.

And the question is, the central question is, is that change related to evolving lung disease or is it related to developmental age? And so the problem that I'm having seeing the connection with is how term or near-term kids who don't have lung disease, how studying those kids will help you answer that question.

And if you could help maybe even reiterate some things that you have already said to make me see the connection there or, alternatively, is there any way or are there any ways that you can modify the control group that may answer that original question more directly?

DR. HAMVAS: Okay. Good question. So I should probably mention that we have had the opportunity in our early study from four or five years ago, where we studied some term babies with "normal lungs," we had the opportunity to study a couple of those babies on several different occasions about two

to four weeks apart. And we know that in those term babies, those two -- it was two babies. We know that their parameters of surfactant metabolism on those separate occasions were identical.

So it gives us the impression that once a baby is born at term, at least over that first month of life or so, that with an n of two and all the caveats that go along with it, that surfactant metabolism seems to be relatively stable.

So with that as a background, that suggests to us that then there are likely to be developmental changes earlier on in gestation, although, again, to what extent those occur, I don't know.

Again, I think that given the realities of the availability of babies who require mechanical ventilation, have reasonably normal gas exchange suggests that we're only going to obviously get a population of term or near-term babies.

We will occasionally have a premature baby who has normal lungs who requires intubation or apnea or who may have one of these birth defects, although my experience has been -- and we have not studied or even approached any of these babies -- our general experience has been that these babies are pretty

sensitive to other, you know, especially surgical manipulations in terms of what happens with their gas exchange postoperatively.

So we have at this point kind of stayed away from those very rare babies who may be premature who may otherwise fit into some of these categories.

I think, again, where we'll get the information in terms of the term or near-term babies is really, again, the relative proportions of the contribution of acetate and palmitate but, more importantly, what is that proportion of recycling or that new surfactant synthesis coming from unlabeled sources.

And, really, using that as kind of the guidepost, we have this ever-increasing contribution of new synthesis to surfactant replacement at 26, 28, and 30 weeks. If we see a distinct difference in the term babies, where there is significantly more recycling, I think we can suggest that there is some disruption of surfactant metabolism in those pre-term babies.

Getting babies who are mechanically ventilated, for whatever reason, between that kind of 30-32-week gestation and the near-term babies is going to be very difficult to come across, especially in

terms of the babies who require mechanical ventilation but have otherwise reasonably normal gas exchange.

I'm not sure if that helped you out or not.

DR. FANT: I'm not sure either, but I'm sure we'll discuss it more.

DR. HAMVAS: Yes. These are all excellent points. And I think that if we could design the ideal study, it would be to have a baby at 26 weeks, at 28 weeks, and at 30 weeks who has normal gas exchange but who requires mechanical ventilation. That would be the ideal comparison group in order to assess these.

And all of the neonatologists in this audience know that you might run across one of these babies every couple of years. So it's a pretty unusual phenomenon in that these term or near-term babies are: number one, more accessible,but, yet, they will still provide us kind of that guidepost as to what normal or near-normal surfactant metabolism should be in the term gestation or the near-term infant.

DR. FANT: In terms of the availability, would it be reasonable, do you think -- in addition to the normal or near-normal kids at term or near-term, are there babies that are at similar gestational age

that incur similar lung injury?

I'm thinking of kids with idiopathic pulmonary hypertension, for instance, that endure fairly high pressure settings and oxygen concentration and acquire lung injury secondary to in a similar fashion to the pre-term kids, although they're at a more mature gestational age, that might be able to be compared to the "normal" kids to get a sense of what injury in and of itself -- I'm still getting back to the point. Is it lung disease or is it gestational age?

DR. HAMVAS: Right, right. We have studied some term and near-term babies with respiratory disease and with just the single tracer acetate. We are still recruiting those types of babies under another protocol.

So we are getting information about what the diseased lung at term or near-term looks like, at least surfactant metabolism by our parameters looks like in those babies.

CHAIRMAN NELSON: Billie Lou?

DR. SHORT: Not to beat the term baby to death, but that really is not a homogeneous group. And I'm concerned about at least the abdominal wall defects. A lot of the kids we get have very

significant lung disease.

And hypoplastic lungs can be a component. Heart babies, the very severe ones, are on prostaglandins and then going to surgery in three to four days. And the neurologically damaged kids, are you guys either in the head cooling or body cooling studies with that?

DR. HAMVAS: Not yet, no.

DR. SHORT: You're not at that point. Okay. You know, I do have concerns about the homogeneity of the group. And then the other, you said the animal data that recycling becomes a larger component very early, within the first 24 hours.

So it almost sounds like you ought to do a second protocol with these term kits because they're so different from the pre-term babies. But does that concern you that if you're going to study the same baby at two weeks or that you may be seeing a differential just related to the term infants' initial metabolism of surfactant? Is that --

DR. HAMVAS: Yes. All of those things that you bring up are things that concern us and we struggle with in terms of trying to develop the ideal comparison group.

And I agree that these babies, these

term/near-term babies, are a very heterogeneous group. We do have that small group of seven babies that we studied with simply acetate previously that can provide us at least a context in terms of looking at what the acetate precursor, acetate contribution is to surfactant synthesis.

If we saw a significant or what we thought was a significant deviation from what we had obtained previously in terms of the acetate, then we would say that this baby probably does not have normal surfactant metabolism, and they would not be analyzed in that normal group. So at least we have some reference point at which to kind of determine do these babies really have -- in retrospect, do they have normal surfactant metabolism?

As far as looking at birth versus two weeks versus four weeks, again, those are relatively heterogeneous groups of babies. Again I go back to the couple of term babies that we had the opportunity to study a couple of weeks apart who had similar indices in that, almost identical surfactant indices in those two weeks.

So those particular babies were probably first studied at about a couple of weeks of age. So they were not in that immediate newborn period

obviously, but at least two to three weeks out, their indices of surfactant metabolism were not changing.

DR. SHORT: Just a couple of questions on the preemie population. The fluid intake you intake to be -- or the infusion will be about 25 percent of the fluid intake. And you're using five percent glucose. Have you seen any -- some of these kids are on higher glucose at that point. Any hypoglycemia as a risk factor in this population?

DR. HAMVAS: No because they're getting glucose through their parenteral solution.

DR. SHORT: So you adjust for that?

DR. HAMVAS: Right.

DR. SHORT: And the tracheal aspirate methodology, obviously your nursery is very used to doing this, but at least many years ago when we did some work with Jeff, it was you were putting down at least two cc's of saline, which was not the norm for our regular suctioning. Is there a protocol that is different than the regular suctioning process that nurses do or is this basically all you're saying?

DR. HAMVAS: Our standard protocol that the nurses use is to have half a ml of saline and then down the endotracheal tube and then suction. So we're using that same --

DR. SHORT: And then just to throw out since you brought up the other trial, I'm assuming these two trials, kids couldn't be in both trials. Is that correct or is that incorrect?

DR. HAMVAS: No, no. They're just enrolled in one or the other.

DR. SHORT: Okay. Thank you.

CHAIRMAN NELSON: Thank you.

I would like to turn now to our open public hearing. Ron, we need to get that done on time. Then we can go back to questions if that's all right. Dr. Hamvas will be here until 4:00 o'clock. So we can tackle it. Thank you very much.

Before we go to our speaker, I need to read the open public hearing statement, "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 Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of

any financial relationship you may have with any company or group that may be affected by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

"Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

So I assume it's still true, although we have 20 minutes left, -- someone could declare themselves wanting to speak publicly -- that Dr. Whitsett is the only such person so far. So you're welcome to come up and address the Committee within this session with your protocol-specific comments.

OPEN PUBLIC HEARING

DR. WHITSETT: I just have a general comment as a neonatologist and a care-giver. It relates to we made great advances in neonatology in the last 20 years, but we really shouldn't be even close to satisfied.

Mortality at 24 weeks is about 50 percent.

Fifty percent of those babies have profound abnormalities affecting neurobehavior in growth in their development. And so there is no time to rest.

The only advances we have made in the last 20 years have come from science. And they relate to resuscitation, nutrition, and understanding surfactant biology and realize that almost all of our insights regarding surfactant biology have come from the study of newborns. We apply what we learned in newborns in the last 20 years to understanding how postnatal lung works. We actually, pediatricians actually, inform the basic scientists about how the lung works.

It's not time to rest. We have terrible morbidities. And our babies aren't doing nearly as well as we would all wish them to. And we need them to reach their genetic potential, not just the best we could do. We moved through a time in which what was our best was unacceptable. And it's still unacceptable to me.

So we have many opportunities. And to me those opportunities come from science. So the most important thing for me -- I don't really do this kind of work. I'm a basic scientist and a clinician. The most important outcome is that we need to find ways of going forward to study these babies. It behooves us

to study them and to study them carefully and well and in accordance with the needs of the families as well.

So this is really a plea for this kind of study needs to be applied to babies broadly about how much sugar we should give them, about how much amino acid, how they're going to utilize it, the drugs we give them. We're going to use mass spec when we study pharmacodynamics because we can't take large blood draws for some of the things we need to do.

So as we improve the care of babies, we really need to be advocates for understanding how to proceed safely with clinical studies in babies.

Baboons. Try to hold down a six-month-old baboon and study him in the intensive care unit for three months on a ventilator. You hold him. And watch out because they have long incisors.

So it would be wonderful if we had postnatal non-experimented-upon live animals that we could study that mimic our diseases in full term. We don't have them, and we don't hold down full-term baboons. They really bite, really terrible.

There is some basic science that we really didn't talk about here that we are really starting to understand. We now understand what some of the biologic controls of surfactant catabolism as well as

the controls of pool sizes and what controls surfactant's function in the air space. We had no clue about this five years ago.

And so I just happen to have data that I'll finish with that pertains directly to this question about the post-term full-term baby. We think we know about it. Full-term babies should have surfactant just like we do. But, remember, the full size of a full-term baby is 100 milligrams per kilogram. And your and my pool is four. So we're going to 100. To do that, we have to change synthesis recycling, catabolism by macrophages type II cells. It's complicated in there.

And just to show you how profound that is, it takes -- I just happen to have the data sitting here while you're talking. So the data are this is a full-term baby mass. This is his full size. This is adult levels of normal pool size right here at two months of age, pretty good.

So the bottom line is we now know that this is controlled by surfactant proteins. It depends on injury. Particularly this is controlled by surfactant protein D, which is absent in babies with BPD.

So there's extraordinary basic science and

complex science regarding macrophage function, pool size control that we don't have a handle on at all. And the only way we're going to get a handle on that is going to be these kinds of study.

As difficult as they are, as inadequate in getting pool size, wow. Boy, computers are getting better. They're getting so smart.

(Laughter.)

DR. WHITSETT: This is the pool size in a full-term newborn two-gram mouse. And he drops his pool size, alveolar and total lung, dramatically but progressively over a two-month period, reaching normal levels two to three months out. This is a little tiny mouse.

We have no clue in the normal human being when we reset that pool size. Why do we reset it? It indicates normal lung function. If we understood that pool size and control of it, can we mimic that in the babies? Do we need to understand it to mimic it? Is that a therapeutic opportunity?

Until we get the basic knowledge that provides insight into these processes in the term baby, as inadequate as it is in terms of precise control, we don't know what we're shooting for in a pre-term baby.

So I am simply advocating for due diligence in providing data that will inform us about the future.

DR. RUBENSTEIN: One question about that. Can you remind me when the alveolar phase of development completes in a mouse?

DR. WHITSETT: At day 15.

DR. RUBENSTEIN: Day 15?

DR. WHITSETT: So it's unrelated to --

DR. RUBENSTEIN: It's unrelated to that.

DR. WHITSETT: Yes. It goes on. You're a mature, breathing mouse at six weeks of age, and you still haven't reset your pool.

Another aside is that there are up to three full differences in these pool sizes among different strains of mice. So your other heredity influences profoundly. Until we begin to understand our baby differences and strain-dependent differences in babies, we're still going to be in a black box wondering "How does this miracle happen?"

And I think science can move forward, and we can understand the issues at hand and not unless we study them safely.

CHAIRMAN NELSON: Thank you, Dr. Whitsett. And hopefully when you give you your computer back,

it will still function.

(Laughter.)

CHAIRMAN NELSON: In looking at the agenda, what I am going to suggest, actually, since this closes our open public session for individuals that choose to speak at the meeting, that I summarize the submitted public comments now. And then that would allow us after lunch to basically just move into our own discussion of the issues. And since they were submitted as public comments, it sort of makes logical sense for me to do that right now.

So I have some slides. And I can speak and just advance them from here.

DR. FLEISCHMAN: Do we have all the public comments?

CHAIRMAN NELSON: Yes, you do. They are in the handout, the handout from today. And they're on pages 13 and following.

SUMMARY OF SUBMITTED PUBLIC COMMENTS

CHAIRMAN NELSON: But just to basically run through it, there were seven public comments. The category of individuals that submitted public comments include one federal government employee; five health professionals, of which one identified himself as an academic IRB chair; and then one citizen, for lack of

a better term. We're all citizens.

Now, in terms of the categories, what I'm going to do is I basically looked at these seven comments. And I tried to group them into specific categories so we can think more generally about the comments.

The three categories that I grouped them in, one is the category of not approve, which I grouped into two: either those who said don't approve it because they misunderstood the protocol or those who said not approve but they understood it, recognizing that this is a bit of a value judgment on my part, which I'm willing to defend; then recommendations and then questions.

So in the not approve, misunderstood, there were two comments. One raised the question of the causality of autism, which I know of no data to support that.

The second basically interpreted a lot of the procedures that were being performed clinically for these babies as research-only procedures. And so I don't think it was clear to that individual that the intubation and the catheters were part of the clinical care.

Then there were two that really didn't

say, but it appeared, at least from their comments, -- and I'm being generous -- understood the protocol and just raised the questions as to whether the risk was greater than minimal and felt that because of that, it could not be approved.

Now, there was one recommendation in one of the comments about the presence of what I'm -- this wasn't the language they used but adapting language from what exists in many institutions that a research subject advocate during the informed consent and conduct of research might be a useful presence as one recommendation.

And then there were three individuals that raised a number of questions. These questions were not raised by all of the individuals but I think fit within the themes that each one of them was raising.

The first general area was the safety of the infusions. And there was one individual who pointed out that, in fact, he gave an n of 60. We have seen an n of 53. I didn't add up to know if this was accurate or not, but that there then would be data about outcomes, adverse events for previous studies, et cetera, the solution being used. And we had seen some of that data. The risk of contamination was raised.

One individual commented on a case in Maryland, which I'm not familiar with, of an adult who had what I assume was endotoxic shock or septic shock as a result of infusion.

And specific issues, methods of assuring and testing for sterility, rapid testing, 24-hour shelf life, training and skill of the personnel, many of which, although in our discussion we may have further questions, I think have been addressed by the presentations we have heard this morning, even if they were not necessarily addressed in the materials available prior to the meeting.

And then there was a question raised of any particular complications if this isotope infusion -- there was some extravasation of that fluid into subcutaneous tissues.

Another issue that was raised and has been touched on in our questioning of the investigators is interference with clinical care, would this interfere with the infusion of other potentially life-saving solutions? What if the isotope was being infused if you needed vascular access for medically necessary products during those 24 hours?

And then there was the question which I think Kate began to raise as well around the different

sampling. What do you do if you have incomplete data. If the infusion, for example, has been delivered for less than 24 hours, is this just thrown out? And what does that mean, if you will, for the overall ethics of the enrollment of subjects when the data you collect from those individuals is, in fact, not useable?

So that is my summary of the material that was submitted as part of the public comment period. You have the text in front of you within the packets that were handed out this morning. And I think that can then inform our deliberations and discussions this afternoon.

So with that, I mean, we don't necessarily have to fill up the next five minutes.

(Laughter.)

CHAIRMAN NELSON: Unless there's something I'm --

DR. JOHANNESSEN: For lunch, you're going to be heading across the street. There's a new buffet eatery across the street. Stan will lead the way.

CHAIRMAN NELSON: Okay. I guess lunch is across the street. So why don't we, then, break for lunch? We will start again at 1:00 o'clock. My intent was that we could move right into questions and panel discussions. So hopefully the buffet will move

expeditiously. Thank you.

I will remind committee members that all discussions of this since this is a public hearing have to be conducted publicly. So lunchtime is not an appropriate time to discuss the protocol at all, so social talk only.

(Whereupon, at 11:55 p.m., the foregoing matter was recessed for lunch, to reconvene at 1:00 p.m. the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:05 p.m.)

CHAIRMAN NELSON: Well, we seem to have everybody with one exception. Our executive secretary is out and about somewhere, but I guess we'll start without him. The copilot seat is empty. It makes me a little nervous.

(Laughter.)

CHAIRMAN NELSON: That's all right, Alan. You're just sitting in the back, right?

Well, let me just set a quick context for our afternoon and point towards where I hope we're going to get. At the end of the day, we need to make a decision that falls into one of three categories with a twist. And let me tell you the there categories and then give you the twist.

The three categories are: approval, approval with conditions, or disapproval. Now, I am reminding you that under the approval with conditions, if we have conditions, I will ask people to state them very clearly. And my interest initially as we get into that process will be go over things that people feel are required, as opposed to it would be nice if.

Now, the twist is before we get to that, we need to have enough of a discussion to have some

sense of which category. Since we're dealing with four different categories of research within Subpart D, it would be highly complex to go through three different options over four different categories. For you mathematicians, that would be 12 different permutations.

So my goal is for us to have an initial discussion at least so we begin to coalesce around the category. And then we can begin to sort of get more concrete.

QUESTIONS AND PANEL DISCUSSION

CHAIRMAN NELSON: And so with that in mind, I'd like to turn to the questions and, with your permission, sort of modify them slightly and just give sort of three general categories I see us working through.

The questions that you see which are under in the book and I think -- are they in this handout? We have a slide. Why don't you put up the slide?

So the specific questions that we presented, I would propose -- I'm not going to read them at this point. And in many ways, if you have been in this business long enough, you know we'll probably bounce back and forth between some risk, et cetera. Once we would answer these questions, place

it into a category. So to some extent, a discussion of those questions will place it into a category.

I think there is a prior question that may merit a little conversation further that we were touching on this morning, which is scientific necessity. Then once we discuss that, I would suggest turning to these questions. And then once we have discussed that, have some discussion about the consent process and documents, and then hopefully turn to the more concrete task.

Now, in doing this, I will remind people that we are not an IRB. It's not our role to serve as one. And we do have to put some trust in the process, assuming that we have provided concrete direction. So I don't even think IRBs are supposed to wordsmith consent documents. I keep that out of meetings. So we shouldn't do that either.

So, with your permission, I would like to suggest that the first sort of arrow we talk about -- and I haven't put in my own mind the times, but I'll keep an eye on how much time we spend and hopefully drive us through to a 4:00 o'clock ending with a task achieved -- will be on a scientific issue because I heard a number of questions coming from our neonatology colleagues sort of thinking about that.

And so I guess I'd like to open us up for that discussion before we actually move into a discussion, then, of the specific questions or maybe there's -- Ron?

DR. RUBENSTEIN: So in thinking about Michael's question before about what are you really learning, developmental versus just maturation versus lung disease, if you think about the protocol, what the protocol needs is a blood-drawing line or the ability to draw blood and the ability to access the airway.

It has been written it's limited to kids who are mechanically ventilated, but I would raise the question about what about kids who have had tracheostomies placed for clinical indications?

These are kids who get routinely suctioned. So we're talking about the former preemie who has been mechanically ventilated for a while but is now weaning off mechanical support. They get suctioned at least twice a day and a term kid who has a paralyzed vocal cord, for whatever reason, or subglottic stenosis, for whatever reason, or severe craniofacial anomalies that require placement of an artificial airway. But they may have no lung disease, may be breathing spontaneously through a tracheostomy.

But, yet, they have access to the airway that would not require sedation, bronchoscopy, that sort of stuff.

So I think what I'm getting at is I am not necessarily abdicating doing that in this project, but I do think that one could start to address the issue of kids who are term gestation but were born prematurely if you do them at 40 weeks post-conception with whatever level of lung disease they have versus kids without lung disease but have artificial airways for other reasons. And I think you could address surfactant metabolism.

The one caveat with that is anybody with a tracheostomy is likely not to have perfectly normal lungs just from the absence of the upper airway filter allows the lungs to get exposed to.

So, for example, they get colonized with different bacteria and so forth. So they wouldn't exactly be normal kids, which I think, you know, helps when you're trying to get to what category you're trying to prove under because if they have chronic colonization in your airway, you could reasonably hypothesize surfactant metabolism might be different and understanding it may be important.

So I just wanted to throw that out as, you

know, a way to down the road try to address some of these issues that we're struggling with from a scientific basis.

CHAIRMAN NELSON: Other discussion? Mark and then Alan?

DR. HUDAK: I'm still trying to understand for the control group exactly how this information is going to be helpful to the advancement of testing therapeutic options in infants who are pre-term.

And certainly I think that as the protocol is sketched, I mean, it clearly involves more than minimal risk, but it doesn't involve an undue amount of risk in terms of the fact that these sort of things are done commonly to other babies who have diseases that are studied.

Blood drawings are very common. The nursery tracheal suction is very common. The nursery infusions are very common. This infusion is in no significant way different than parenteral nutrition solutions we administer to babies on a routine basis. So I don't see that it is very different from a lot of the things we do.

The issue is really the scientific knowledge issue at this point. And in this control group, I'm worried about if we find out the

information, it may be homogeneous or not. It may indicate something about surfactant metabolism that basically confirms the suspicion, which is that in the term baby, there is a lot of recycling that goes on.

On the other hand, it may show that in these kids, for whatever reason, that is not the case. And trying to grapple with those two things and looking at interventions, the two interventions that I heard were, well, maybe we can improve the nutritional care of these babies so that we replete their surfactant in a better way.

And to the extent that they are surfactant-deficient, either functionally or metabolically or in terms of pool sizes, it doesn't seem to me that what you find out in the term infants is going to alter your structure of your clinical study on that respect because you can never assume that your intervention is going to be either safe or effective. And it needs to be tested in any case. I'm not sure it generates an additional hypothesis. And we don't know anything about surfactant pools, and this particle doesn't address that either.

And then in terms of the other issue as to whether or not it's better to treat with a surfactant that stays in the alveolar pool and isn't recycled or,

conversely, you know, you want to have a surfactant that maybe does go into the recycling mode, I'm not sure that there's an alternative you're going to do other than study those preparations. And what you find out in this group of term control babies I'm not sure is going to change how you approach that hypothesis either.

So I guess that's sort of my dilemma here. I think it's reasonable research to conduct. Information is good. Knowledge is good. But under the context of 407, as I understand it, there has to be some concrete prospect that the knowledge in this population is going to enhance development of good interventions in other babies. And I just can't make that leap at the moment. Maybe someone can help me with that.

CHAIRMAN NELSON: Mark, let me ask you a couple of questions. If you look at the slides, page 43, there's a hypothesis that's presented, "A decrease in surfactant recycling over time is associated with the evolution of chronic lung disease, rather than the normal development in premature infants."

The argument, as I heard it, was that the comparison group is necessary as much pragmatically because of access, as Ron pointed out, but as an

attempt to try and answer that hypothesis.

Four-o-seven does allow just something for understanding. It's a serious problem. It doesn't necessarily say it has to be an immediate leap into an interventional strategy.

So I guess concretely, do you think as designed, as proposed, this hypothesis is addressed by having that comparison group or not?

DR. HUDAK: Well, this is part of the dilemma. For instance, suppose you do find that in term babies, you have, you know, predominantly recycling going on and very little of the sort of de novo synthesis from these precursors. Well, that's, of course, the hypothesis.

On the other hand, if you find that there's a lot of non-homogeneity there and, in fact, in some of those patients, they do have a lot of incorporation of precursors and that may be for a variety of reasons that one will speculate about, that doesn't refute the hypothesis either. So in either case, it seems to me you would probably have to test this hypothesis with the clinical intervention study.

And the second issue is so it doesn't in my mind alter the need to study this hypothesis. Will that information help you modify how you would go

about designing a protocol? Would it be useful in that sense? I can't get there either. So I'm still confused as to how that information is going to help us with a pre-term baby.

Is that clear or --

CHAIRMAN NELSON: Before Mary Faith, Alan, you were up.

DR. FLEISCHMAN: Yes. I would like to back us up to the regulations a little bit. I know that you are going to get us there, Skip, but if we look at page 127 of our book, where I'm looking, 406.407, I guess we could look at the FDA comparability, but they're identical, I understand. Right?

CHAIRMAN NELSON: With two exceptions: clinical investigation, instead of research; and documents.

DR. FLEISCHMAN: The standard in the 407 assessment is the research presents a reasonable opportunity -- underline the word "reasonable" -- to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

Clearly, we're dealing with a very serious problem affecting the health and welfare of children:

respiratory distress syndrome. And at least I'm convinced in terms of the science presented, that there's a level of reasonableness about the opportunity to further the understanding. And it is I think only furthering the understanding. It will lead perhaps to other studies that can help us with either prevention or alleviation.

And I think that's a very low standard. In fact, it's a lower standard than the standard the IRB has to use in the 406 context, which is vital importance.

I don't think this study is of vital importance, but I think it is a study that presents a reasonable opportunity to further understanding. And it's an interesting regulatory question, but we are faced with trying to interpret the regulations as they exist.

I do agree with the IRB that it was not approvable, if that's a word, at the local level based on 406. I don't believe that the comparison group, the normal, so-called "normal," full-termers have a condition or disorder that would place them in 406. Yet, I do believe that the risk level fits the minor increase over minimal. And the commensurability standard I think is fine.

So I am left with this problem for me of I don't think this is a critically or vitally important study, but I do think it's a study that gives us a reasonable opportunity of learning something about this disease with a fairly low level of risk.

CHAIRMAN NELSON: Mary Faith?

DR. MARSHALL: Well, Alan just opened the door. I was going to raise the same question, but I may have a different perspective about what the phrase "health or welfare of children" means. So I'm asking. I haven't made a concrete decision.

When I think of health or welfare of children, I guess I'm thinking of children in general, not children who are premature or children who have respiratory distress syndrome. So I'm not sure that what we're talking about perhaps doesn't necessarily, at least in terms of the research group, not the control group but perhaps even the control group, fall under 406.

But if someone could help me understand how the research question if it has to do with, you know, developmental understanding, then I could be persuaded that perhaps it's a general problem that would affect children? Maybe I'm wrong.

CHAIRMAN NELSON: I guess I'm a little

confused. It's not clear to me at least that the phrase "children" is meant to imply that the health problem has to extend to 100 percent of the pediatric population, as it does to --

DR. MARSHALL: I'm not saying that it has to. I'm not saying 100 percent of the population, but I guess I'm just wondering what the difference is here between 406 and 407. And perhaps someone could articulate it clearly.

I have a question for Mark. And you may have answered this, but is there a second study here potentially, would you see, as opposed to having a sort of strangely defined control group here? Is there an hypothesis that would support a second study with a larger n that might answer the developmental question more concretely?

DR. HUDAK: I think Aaron can talk to that better than I can, but I think what he sketched out as the best study is the one that has the controls at the same gestational age. And that is a study that is not impossible to do, but it would take a long time at any one institution to accumulate those rare babies to answer the question.

DR. MARSHALL: But in theory, it could be done perhaps with other if it were a multi-center

trial or --

DR. HUDAK: In theory, yes.

DR. MARSHALL: Yes. Okay.

CHAIRMAN NELSON: Mary Faith, to comment on your question about 406 or, for the FDA benefit, 53 versus 54, in this particular project, there were infants enrolled who clearly had a condition. prematurity with lung disease associated with that, where information was generated about surfactant kinetics in that context under the category of minor increase over minimal risk.

And at this point, the investigators are saying, "We're not sure how to interpret what we've found without extending that research into a group that does not have that condition that we had originally studied." And, therefore, because they don't have that condition but they have other reasons to be intubated because of the access issues, it doesn't fit under the minor increase over minimal risk with the condition category. That's very different. And, therefore, it's thrown into 407 or 50.54.

The broader question about what the language of the health or welfare of children means relative to that category, I know of no particular insight on that other than saying, "Is it a big enough

problem for enough children to sort of justify going forward as long as it can be conducted ethically?"

And I would venture a guess that premature birth is a big enough problem that trying to understand that data with a comparison group in my view would fit that health or welfare of children model. I mean, it's a pretty broad population. I think the statistics we saw that Dr. Whitsett presented were quite large. And that was just in the United States.

So those would be my thoughts.

DR. MARSHALL: We've visited this on other 407 panels. So I just wanted to put it out on the table and make sure that we were in agreement about the scope of the problem.

CHAIRMAN NELSON: Billie?

DR. SHORT: Yes. I just want to echo the presentations. I think the prematurity issue is a huge one, financially. These kids are in the hospital an average of two to three months. And that is an enormous cost. And the numbers are significant. Actually, the prematurity rate is going up and not down due to we think a lot of the in vitro fertilization, multiple births.

So it's a very big issue. And this

hyaline membrane, the treatment of this is a very big issue. We've made huge I think advances with surfactant being given down the ET tube, but we still see this group of kids go on and have this terrible lung injury.

I think where we're going to have huge breakthroughs in neonatology is in nutrition. Dr. Whitsett kind of alluded to this. We don't know what we're putting in hyperalimentation. Is that appropriate for lung growth and brain growth?

And we need to start digging into that. And it's a very difficult area. So I think the proposal is very important. I think the concerning thing is the term population. Is it consistent enough to give an answer or is it too heterogeneous?

That's a group that actually is fascinating to me also. Those kids, many of the kids, can go on and have actually some lung disease and have a different phenomenon going on.

So I would like to see either a stricter definition of that term group, taking out some of the kids who could be outliers, like the omphaloceles that have very significant hypoplastic lungs should not be included because they are different than an omphalocele who is just on the ventilator because he

had surgery and really narrow that down. I think that makes the numbers smaller, that potential problem.

The trait kids, at least in our institution, are enough to really answer the question I think, but I think the premature population in the study is it's a very, very important study for our growth over understanding mechanisms and how we can maybe change this disease, just by a nutritional component. So I think answering metabolism and trying to look at it as best we can with all limitations is a very important question.

CHAIRMAN NELSON: Mark and then Ron?

DR. HUDAK: Well, I guess let me back up a minute here. I do want to say that the study as presented does in my judgment present a reasonable opportunity to further understand. That doesn't mean that we are definitely going to have a better understanding. We might have a better understanding, but it's a reasonable opportunity to have a little better understanding.

The issue about nutritional studies and these other studies, I think a full justification for those things I don't see being made by this research alone.

We don't have anything on pool sizes to

look at. We don't have really a whole lot of information, what's going on or not going on with recycling, other than it becomes less as these pre-term babies on ventilators get older.

It may be that an appropriate intervention is to supplement babies with palmitate precursors because maybe that is the -- maybe the babies are really surfactant-deficient and the way to make them more surfactant-replete is to nutritionally supplement, put more surfactant in that pathway, rather than take the attitude, "Well, you know, we need to start interfering with or beefing up recycling."

I think the biological system is very, very complex. And I think that we can generate hypotheses but realize that any hypotheses we have, no matter how much knowledge we base it on, still needs to be tested. And the results are not predictable.

CHAIRMAN NELSON: Ron?

DR. RUBENSTEIN: So a couple of points. One, it's not clear to me that the term group doesn't have a condition. They have a condition that requires mechanical ventilation.

I think my understanding of the evidence on surfactant metabolism is that any kind of noxious

stimulus can change surfactant metabolism. So it may be that we get valuable insight from that group into surfactant metabolism from doing this experiment.

The second is sort of in response to Mark's first statement, which is Mark raised a series of questions that we don't know the answer to in his discussion of things that he was concerned about with the protocol. And we won't know the answer to those questions until we do the protocol.

I think there's enough uncertainty about what's going on to say that we don't know the result. And that actually makes people who do investigation rather uncomfortable when they don't know the results. And it certainly makes study sections uncomfortable when they think.

But I think, you know, acknowledging that there may be alternate answers that come out is the hallmark of a good research design because then you sort of say, "Well, if it comes out the way I don't expect, then I can go look at the alternate hypotheses and generate more knowledge." It's okay that a hypothesis is wrong. Okay?

CHAIRMAN NELSON: Thanks. I might point out, Ron, you raise an interesting dilemma by your point about intubation alone potentially altering the

kinetics of surfactant because if the emphasis then is on the condition of being intubated and the perception is that the risk appropriately is categorized as a minor increase, then you could go forward. But that very argument undercuts the comparison of this group with the previous studied groups.

So mainly because the access requirement that you have, which is intubation -- and we're not going to say, "Go intubate kids who don't need intubation --

DR. RUBENSTEIN: No. And I'm not saying that at all. What I'm saying is that if you're looking at infants who require mechanical ventilation for a pulmonary versus a non-pulmonary reason, you can -- and this is why I said you really should call this a disease control group, as opposed to a normal control group because then I think you get closer to 406.

And I agree with Billie that there are going to be very few kids with tracheostomies, but that does give you the opportunity to try to get some kids at the same gestational age so you're not just doing the preemies when they're 32-34 weeks post-conception but you now have the opportunity to expand it and do it at term post-conception and

compare them directly by expanding the protocol a little bit.

I think this gets to some of the issues that are troubling Mark. And then I think we can get more meaningful data by potentially expanding it a little bit.

There is going to be no perfect group to do here, but --

CHAIRMAN NELSON: Let me pursue you a little bit, Ron, because I think you're raising an interesting question. Generally I have understood disorder or condition to be defined relative to the protocol's primary investigation. You can have a child with a condition that is unrelated to the scientific investigation or the question you're asking. And you wouldn't say they have a condition for the purpose of that protocol.

So are you suggesting that they basically reframe their hypothesis in a way that defines the children they want to include that the IRB had determined couldn't be included under 406 or 50.53? Are you suggesting they redefine the hypothesis to where those children then have a condition? Is that what you're suggesting?

DR. RUBENSTEIN: Well, I'm not necessarily

suggesting that as the way I view this protocol because to me, as I read the protocol, the issue that the IRB had that didn't allow them to approve it under 404 was the risk of infection with the infusion. Okay? That was what was written in the IRB minutes.

You know, an IRB, even though it's not in accordance with exempt guidelines, my understanding is that an IRB can look at a volume of blood drawn and decide that yes, that's minimal risk, even though it doesn't fit within the exempt guidelines.

So I was really sort of thinking about my review as trying to figure out exactly what is the risk of infection because that is the risk that was identified by the IRB, which is why I specifically asked what does "extremely rare" mean? What are your numbers on infection? Because I feel almost if we can quantitate that that risk is truly a minimal risk of infection, then this might actually be approvable under 404.

DR. HUDAK: Well, I would just like to speak to that. I think the answer to that question is really not known. And I can't conceive of a way to sort of tease out that information, the issue being that a lot of these little kids who are 24, 26, 28 weeks who are on TPN have frequent staph epi

infections, other infections, bloodstream infections, and to piece out how much of that is due to the infusion, which they need because they're pre-term, versus how much is because they are pre-term and their immune defenses are low. There's no answer to that question.

So the risk, I mean, in this population that you looked at, may be low in terms of the percent of babies who sustain a bloodstream infection. But why did that baby get that infection?

CHAIRMAN NELSON: So we have touched on, in spite of hoping to take this sequentially, question 4, question 2, a little bit of one, maybe some in 3.

So why don't we just focus in on this categorization of risk? And my interest here is, I mean, we can go around and around. And also, you know, risk has some ambiguity relative to the regulations versus what some guidelines have suggested it be interpreted as.

But Ron has specifically raised a question about categorization of risk. So what would be useful for me in terms of minimal risk, minor increase over minimum risk, and for those who aren't familiar with those categories, we would also talk about them a little bit. But let's just focus on identifying the

risks, the rare risk of infection, something that is less than two percent.

The risk of the blood volume draw since there is no additional catheters nor blood sticks taking place, there is no increased risk of suctioning. And that's being done by clinical routine.

And the risks that were addressed about the infusion itself in terms of hypernutermia, a change in acetate infusion, the sort of metabolic and electrolyte risks and the like, I guess the first question, am I missing any risks that I'm thinking about that people would feel would need to be on the table before we say, "Well, how would we categorize those?"

So why don't we just focus on that question? Where would we put that in thinking about the category of minimal risk, which is defined within the regulations as that degree of risk which is no different than the risks of everyday life or in the routine psychological or physical examinations or tests? It doesn't say of who, but some individuals feel that should be of healthy; i.e., non-diseased, children. But that's ambiguous. That's minimal risk. So if it's not that, then it's something else.

So how about just on that point? Is there anyone other than Ron? Anyone think we ought to say this is minimal risk? I'm not even going to say maybe Ron. Angela?

MS. HOLDER: I have a question, if I may.

CHAIRMAN NELSON: Okay.

MS. HOLDER: What risk can you tell me if these children were not in this study and they were just getting ordinary care for their prematurity? They would clearly have some risk of infections, et cetera, et cetera, which are acceptable in the light of treatment of their condition. So how much additional risk are they at because they are participating in the study? That's the question I want to know.

CHAIRMAN NELSON: Well, 2.5 milliliters is -- a full transfusion would be 10 cc's per kilo. I think a lot of IRBs would consider less than two per kilo not a problem for single draws. This is two and a half over a day on a one-kilo baby. For a term, that would be then a third of that because there are generally three kilos, which is a relatively small volume.

I was curious, although I assume they didn't collect the data. They could have looked at

the risk of transfusion relative to the study patients and non-study patients, but I suspect it would end up being no difference, similar to all the other ones.

And the infection on that data-monitoring plan was no different, though the numbers are small. In fact, you could -- and I say this somewhat tongue in cheek -- argue that the infusion benefitted the study group to a p of less than .05, but I'm not sure the investigators wanted to make that claim for their infusion.

So it's not clear to me there is a big incremental risk to this group. Is that where you're going?

MS. HOLDER: Yes.

CHAIRMAN NELSON: Alan?

MS. HOLDER: Skip, I agree with you there is not a big incremental risk to this group, but I don't think this research study falls into the minimal risk category.

And I think these investigators have done an exceedingly fine job of keeping the risks minimized. But it's an additional creation of an intravenous nutritional solution.

Now, that doesn't mean that these babies don't get that kind of intravenous solution, but it's

another one. And, you know, I do think they have done appropriate work to minimize risk, but I would be hard-pressed to argue that this could fall in any stretch of the minimal risk definition.

But from a clinician's perspective, this is a very low level of risk, incremental risk, from a clinician's perspective. But from a regulatory perspective, I don't think it's minimal risk. I think it very comfortably falls into minor increase over minimal risk and may have aggressively minimized risk. And they have done it I think, you know, very, very well.

CHAIRMAN NELSON: Let me go to Billie Lou, and then I'll come back to Jill.

DR. SHORT: Yes. Actually, I just want to agree with that statement. I think for a clinician, you would be in the middle risk category. Again, for regulatory, it's probably above that, but this basically is another hyperal solution. We have lots of data. In fact, the albumin amount is much less than some of these kids may get.

So the infection risk I think for that is very, very low. And the blood draw is small. It's a risk, but it is small. So I think it's a --

CHAIRMAN NELSON: Joan?

DR. CHESNEY: I was just going to agree that I think it is minor increase over minimal risk because you are giving over 24 hours a unit of albumin and with the inherent risks of that, that these infants wouldn't otherwise be getting. So I agree with Alan they have minimized the risk, but there is an increase over not receiving a 24-hour infusion of albumin.

CHAIRMAN NELSON: Let me ask the group a question, then. My preference in getting to where we discuss specific conditions, they should do this, they should do that, I mean, and all the kinds of things that we may want to do would be to do it in the context of a specific recommendation about where this could be approvable if we're going to go there, as opposed to disapproved.

So I guess my question to the group is, do you feel that we need to spend more time together framing these various questions or are we at the point where someone might be willing to venture a proposal of one of those three that I've outlined, either approval, which means no conditions; approvable with some conditions; or reject but specific to the category?

So let me just ask first if people feel

comfortable going in that step or if we need to have more discussion about things to where we could at least fit it within that framework. Alan?

DR. FLEISCHMAN: I like where you're going, but I would like to caution that we first focus on Drs. Spence's and Hamvas' protocol, not re-create it at the outset, and see where we can go with that.

CHAIRMAN NELSON: That's my intent. Yes.

DR. FLEISCHMAN: Okay. Because what we have had are some suggestions to enhance either the science or the doability issue. I mean, it strikes me that we have something in front of us that we need to --

CHAIRMAN NELSON: Right. Procedurally my intent would be if a suggestion like that didn't get an overwhelming round of support as a requirement, it would basically go fizzle. In other words, when we get into that discussion, it is going to be okay, that's nice as a suggestion, but is it a requirement or not?

I'd really like to do that first, get those absolute things on the table. If there are finer points, we can think pick that up as we go along. Does that make sense? So yes, I'd like to stay with the protocol concretely.

Joan?

DR. CHESNEY: Are you looking for somebody to make a motion? In other words, I would favor supporting discussion of approval with conditions at this point in time, I think. Is that what you were looking for.

CHAIRMAN NELSON: But the question is under which --

DR. CHESNEY: You're looking for a consensus?

CHAIRMAN NELSON: No, no. A motion is fine, but under which category?

DR. CHESNEY: Under 407.

CHAIRMAN NELSON: Or 50.54. Our FDA colleagues I'm sure would like us to include that in there. So I guess the motion is for approvable with conditions under 50.54 or 46.407. Now, procedurally we need a second.

MS. HOLDER: Second

CHAIRMAN NELSON: All right. Now, what we end up doing is let's talk about the conditions because the idea here is we get the conditions to where we agree on those and then vote on the main motion once those conditions are in place. So why don't we go through those conditions?

And so what I would like people to do is first talk about conditions that if that were not done, you would basically say it should be rejected. In other words, not it would be nice if, but if they didn't do this, it should not go forward.

Once we get those on the table, then we can go to the next group, which is in doing this, it would be nice if they did this and then get some sense of those.

So the first conditions I would like to entertain would be those things that if they didn't do it, you think it should sort of stop here if they didn't do it. In other words, as it is presented, if they didn't do it, it shouldn't go forward as presented.

Mary Faith?

DR. MARSHALL: I am worried about whether it's adequately powered. And so I would want to be reassured that it was adequately powered, especially the control arm, with an n of ten.

And perhaps one way, we could talk about whether a DSMB for the study is something that should be considered, but the powering I think need revisiting.

CHAIRMAN NELSON: I'm only pausing because

I'm thinking how one would formulate that. I mean, other than asking for an independent statistical review, how would we focus that?

DR. MARSHALL: Yes. I think that would be the way to do it. I think that would be absolutely the way to do it. It could be either done separately with an independent review, statistical review, or if we at some point decided to recommend that there be a DSMB, then they could also prospectively review it. And then their statisticians would obviously take a look at that.

CHAIRMAN NELSON: Let's keep the DSMB separate.

DR. MARSHALL: Okay. Yes.

CHAIRMAN NELSON: So I guess the recommendation for a condition is that the appropriate sample size of this comparison group be reviewed by an independent statistician to ensure that, in fact, the sample size is appropriate.

Now, I assume you are concerned it is too small. Is there a size that would worry you about being too big or is it just a question of power?

DR. MARSHALL: It's a question of power.

CHAIRMAN NELSON: Mark?

DR. HUDAK: Gee, I guess I take a very

different approach to thinking about this. I think that the numbers are very small. I think that ten patients may take by past sort of performance two years, two years or so.

And basically the information you are going to get out of this is -- I mean, your hypothesis may be that compared to the four weeks post-birth in the pre-term infants, this group is going to have very good surfactant recycling. And it's going to be homogeneous because the kids don't have any gas exchange abnormalities. And, therefore, presumably surfactant is intact, in which case to me power is not very important.

You are basically going to see what you find. And if you find that all ten babies have predominantly recycling and very little incorporation of precursors, you have answered your question.

I don't know that a power calculation is necessary to justify the sample size. I think you are going to look at ten, see what you got, and go from there.

DR. MARSHALL: So is that generalizable, then? I guess I'm worried about accrual, too.

DR. HUDAK: You don't know until you find out. That's the whole issue. I mean, that's science.

They may find something very different than what they expected. They might find exactly what they expect.

DR. MARSHALL: So would that argue from your perspective for a DSMB in terms of looking at the findings of the results as one goes along?

DR. HUDAK: No, no.

CHAIRMAN NELSON: Michael wants to jump in.

DR. FANT: Yes. Let me start off with going back to my prefacing comment that as a clinician and an investigator who does investigation because of the limitations of what we know clinically, this line of investigation, while there is no immediate payoff that you can sort of see in the near-term, this type of fundamental increasing our fundamental understanding of the biology of lung disease, both from a developmental standpoint and in different cross-sections in time, you know, I think is very important. And it really pushes us beyond what we have kind of been relegated to trying to deal with and do in the clinical setting now and really addresses some of the more dynamic, complex issues related to lung disease and how best to attack it.

So I think in terms of the information that will be gleaned from any of these kids will at

some level be applicable and generalizable to kids in general.

I know the focus in the protocol, the primary problem that we deal with is RDS in pre-term kids, you know, but lung disease affects kids and adults, actually, of all ages with various underlying disorders. And I think understanding how surfactant metabolism is altered I think at the end of the day is going to be relevant not only to kids but to everybody.

Now, having said that, coming back to the protocol specifically, you know, again, I really don't see how the control group is really going to answer any specific question, really help clarify with this group what observations are made in the pre-term group with RDS. But, having said that, I think the information that's gotten from the term kids will be useful and generalizable on some level.

Now, getting back to the protocol, in the consent process, the term kids are enrolled. The general sense I've gotten is that when they're enrolled, you know, the families may get the impression that somehow the information that's obtained with their kids may help understand what goes on with what's going on in the pre-term kids. And it

may or it may not, but I don't think it will once the data is obtained.

I think kind of at the end of the day when a lot of studies are done, you know, it all may be put together. And, sure enough, it helps us understand the big picture. But I'm not sure that the connection between this control group and understanding the process that's going on in the pre-term kids is going to be better defined or more clearly understood.

And I'm not sure if the enrollment of the control group should be marketed in a sense to that end. I'm not sure if it's -- you know, I think it's just as appropriate and I think it's just as compelling to say this is a problem that affects kids, certainly more strikingly in the pre-term kids, but the information we get is really going to be a critical piece of the puzzle that helps us understand how disturbances in surfactant metabolism affect all kids with lung disease.

So that kind of touches on a couple of areas, one of which from a pragmatic sense is sort of in the consent process.

CHAIRMAN NELSON: Well, then when we finish with the statistician, I'll come back to you and ask you to formulate your consent issues as a

recommendation.

Let me try to frame the question to the statistician this way and then ask how we want to proceed. Even if you see this as a descriptive study of full-term infants, the question of the heterogeneity or homogeneity of the population could be reformed as how many measurements do you need to make to where you end up with a small enough confidence interval to where you can actually have some reasonable accuracy, even as a descriptive predictor of what you would expect in that population when you measure the next infant.

So it goes to the heterogeneity. It goes to the measurement issue. And it's also then by framing it that way not a question you can answer a priori as if you already have two measurements in a population, can do a sample size because you're postulating a difference, et cetera.

So it's kind of hard, even if you view it as a descriptive issue, to say what that sample size ought to be because if it's a very narrow range of measurement, then it could be a very small number. And if it's a wide range, it may have to be a very big number.

So, having said that, I guess my question

is, where do we want to go with that? We could just say it's a concern and not make it a condition.

But having listened to this, Mary Faith, what would you like to do?

DR. MARSHALL: Well, I'm not a statistician. I just have sat on enough sort of intramural DSMBs and so forth to realize that things aren't always well-designed up front.

And if you find yourself in the middle of a study that hasn't been adequately defined or powered up front, then it can be an unfortunate thing.

But if you're saying that this is descriptive and that it's something that will need to be sort of understood as it progresses, then I will certainly defer to the clinician scientists.

DR. HUDAK: I think there's some element that there is a hypothesis, but it's also hypothesis-generating.

DR. MARSHALL: Perhaps just to get back to what you said, at some point I'd like to visit the idea of whether the design of a control group versus whether we really have two separate studies here, I'd like for us to discuss that at some point, Skip.

CHAIRMAN NELSON: Well, let me first add, do you want to reformulate or just decide to take back

the study session?

DR. MARSHALL: I will retract my sort of statistician query, then.

CHAIRMAN NELSON: To comment on the one study/two study thing, you could do it either way. And I think as long as we recognize what it is and evaluate it as it is, it's a comparison group, which is very different than saying it's a control group.

DR. MARSHALL: I agree. I agree.

CHAIRMAN NELSON: So I'm not sure we need to do that. You could have done it either way.

Alan?

DR. FLEISCHMAN: I think Mary Faith, though, is going in a direction that would have recommended a year ago to these investigators. It is clear that the preemie studies are approvable under 406. It is also clear to me that the full-term baby studies are approvable under 406 if these investigators were interested in fundamental questions about surfactant synthesis in babies who are sick and on respirators.

There's a lot of fundamental questions we haven't answered in that population. Now, they haven't sought that from us nor from their IRB, but it strikes me that if their focus had been on this other

context of fundamental interests, we wouldn't be here.

And then if you've got data from the preemies and you've got data from the full-term babies, nothing stops you from kind of looking at them.

But in this context, I think we're at a 407 juncture. And I don't find any deal-breakers. I don't find any things that we need to have in the protocol that isn't there now that would make it approvable that doesn't make it approvable now.

CHAIRMAN NELSON: Okay. Let me see if there are others who might formulate a deal-breaker that needs to be unbroken. I'll go to Joan and then Billie Lou.

DR. CHESNEY: Under the conditions -- and I think Alan makes an excellent point that if you reframed the question, maybe we wouldn't be here -- in reading the materials we had before the meeting and then hearing things today and particularly hearing Dr. Hamvas' comments that just sheer forces and oxygen may affect surfactant concentrations, I am wondering whether all normal newborns who were on a ventilator for non-pulmonary reasons are appropriately included.

And specifically I wonder about if patients who are on a ventilator for heart conditions

should be included. I don't know enough about cardiology and pulmonary medicine, but maybe those of you who do.

I have less problem putting the babies who have GI conditions or neurologic conditions; for example, physical abuse or something like that, but I just wondered if we shouldn't ask the investigators for a little bit more definition of what normal neonates will be looked at other than just having a normal chest X-ray and an oxygen requirement of less than 30 percent.

I guess that's a question, rather than an actual condition. And I don't know if Dr. Hamvas can still comment or some of the neonatologists or Dr. Rubenstein.

CHAIRMAN NELSON: He can if we ask him to. He can't if we don't.

(Laughter.)

CHAIRMAN NELSON: Ron?

DR. RUBENSTEIN: I'll be happy to comment. I think Dr. Hamvas this morning talked about how he would be very leery of children with certain congenital heart diseases being appropriate for the study or not.

I can think of children with vascular

rings who could certainly be appropriate for the study, children with coarctation of the aorta who would be appropriate for this study, children with small non-hemodynamically significant ASDs or VSDs who might be appropriate for this study, but certainly children with tetralogy of Fallot or more complex than that I think that the investigator in this discussion this morning was very succinctly in saying that he would be very leery of putting a patient on this protocol. So asking him to define that in writing, I think he's be happy to do that.

DR. CHESNEY: That was my only point. And maybe that doesn't even qualify as a condition but just that that was more clearly delineated.

CHAIRMAN NELSON: Billie Lou?

DR. SHORT: Actually, that was the same point I was going to make. I would make a condition. I think it's key if you're going to leave this as a quasi-controlled group that you have it very focused and defined. And I think major cardiac lesions with shunt physiology should not be included. I think the omphalocele, the kids who have hypoplastic lungs should not be included.

And I think if they can focus this, there is a group that is on the ventilator with another

disease process with ventilation because secondary to surgery that they could get good data from. And it would make that a cleaner data set if they don't want to add a whole other study looking at term infants with various diseases. And I think if we have to look at this protocol, that would be my recommendation.

CHAIRMAN NELSON: Let me summarize what I have heard for my own benefit and see if everybody agrees. In a sense, we're looking at two sides of one coin in that we're flipping it back and forth. You look at one side as presented.

As a comparison group, they need to reduce the heterogeneity that they potentially may have from other complicating conditions, whether it's various non-pulmonary lesions that then result in pulmonary hypoplasia or cardiac lesions where flow through the lungs may be affected in a way that might impact on surfactant physiology.

Now, to the extent they want that group to serve as a comparison for this other group, they need to reduce that heterogeneity. And I've heard and I've heard no disagreement that then that could fit appropriately under the 407 or 50.54 category.

The irony is that there is, in fact, as the very desire to reduce heterogeneity illustrates,

important questions of surfactant kinetics and physiology in full-term infants with a range of other conditions that impact on lung physiology, not the very least of which is the simple active intubation for a non-pulmonary indication.

And the irony, which I am perceiving, -- and now I am understanding I think better where Ron was going -- the irony that if they had focused on that as their primary hypothesis, then it very well may have fit under a 406 or a 50.53 category because then the focus of the scientific investigation was precisely on that full-term population, rather than as a comparison group for another set of questions, illustrating I think the dynamic relationship between the hypothesis and focus of a scientific investigation and the definition of the condition that you're, in fact, investigating.

Did I get it? Okay.

(Laughter.)

CHAIRMAN NELSON: Hopefully someone has written that down. It's on tape.

But that leaves us with what they have proposed to do and I think, back to Alan's advice, leads to what they propose to do. And I think they've certainly heard the scientific discussion.

It's not clear to me that we have to frame it as a condition. And, you know, the process by which this goes through will be another vetting by the IRB and by the OHRP and by the et cetera, et cetera. So it's not clear to me with this discussion we need to take that and frame it as a condition, having had that discussion.

So, again, placing aside the consent for the moment, which I will give some space to, are there things that really ought to be there that we haven't seen for us to be comfortable with them doing this under 407.

Okay. Let's talk about consent, then.

DR. MURPHY: Now, Skip, did you just say that the condition that Dr. Short thought should be there, you're saying shouldn't be there?

CHAIRMAN NELSON: Well, I mean, we could formulate it as -- I guess we could formulate that to the extent that they want this to serve as a comparison group. The full-term infants that are selected ought to have conditions that are excluded, much along the lists that were mentioned verbally. I mean, that would be fine.

DR. MURPHY: Okay. Because I do think it also gets at some of the other questions that were

coming up earlier so that it makes it easier I think to frame what you just said, which is --

CHAIRMAN NELSON: Right. You're right, right.

DR. MURPHY: -- this group really has questions and we don't want to muck it up by having more heterogenicity in that group.

CHAIRMAN NELSON: Yes. You're right. To the extent that the investigators --

DR. MURPHY: Excuse the technical "muck" word.

CHAIRMAN NELSON: That's an FDA word, yes. I guess to the extent that they're presenting it as a comparison group, making sure that the population is homogenous enough to make it a meaningful comparison group is an appropriate condition.

So I guess, having said that, is there a second?

DR. CHESNEY: (Raising hand.)

CHAIRMAN NELSON: So is the second for the condition, I guess. Is there any other discussion of that particular condition?

DR. SHORT: I'll second it.

CHAIRMAN NELSON: Well, you're the first author. So, to restate it clearly, it's to say as a

comparison group within the framework presented for the research as a 407 is a comparison against a pre-term, that that needs to be a fairly homogenous group explicitly excluding conditions known to be associated with impacts on surfactant, such as cardiac lesions that affect pulmonary blood flow and pulmonary hypoplasia.

Can we be more specific, Ron?

DR. RUBENSTEIN: I think you're going a little far by saying "conditions known to" influence.

CHAIRMAN NELSON: Thought to?

DR. RUBENSTEIN: The major issues I would say, you know, I was thinking kids with pulmonary hypoplasia are going to be excluded from this study because they're not going to have normal chest X-rays. And they're not going to have fractional inspired oxygens less than 30 percent.

CHAIRMAN NELSON: Right.

DR. RUBENSTEIN: So I think they're pretty much excluded. I think you could make the same argument for kids with significant congenital heart disease, that they would already fall out, but if you wanted to say, as you said in your presentation this morning, Dr. Hamvas, that you want to exclude kids with significant intracardiac shunt physiology. And I

do believe the kids with pulmonary hypoplasia would be excluded by what is here already.

So if you want to just get to the kids with significant cardiac shunt physiology, that would I think take care of -- I don't think we know enough about surfactant metabolism to say things that are known to influence surfactant metabolism.

CHAIRMAN NELSON: Mark?

DR. HUDAK: Well, I agree with the discussion, but from what I heard Dr. Hamvas present, I think he had well in mind exactly which patients he was going to put in this comparison group. And I think sort of better defining that is perhaps better left to the local IRB than as a condition of approval here.

CHAIRMAN NELSON: I guess we could word it generally enough so we're not micromanaging that population. And I'll have to capture the wording. Is that fair without listing conditions but express the sentiment?

So just on the one condition before us, which is that the population be defined in the way it was presented to us, homogeneously enough to make it a meaningful comparison group, I guess I'll just ask for hands of those who are in favor of that as a condition

for approval.

(Whereupon, there was a show of hands.)

CHAIRMAN NELSON: I'll let the record stand. Are there any abstentions?

(No response.)

CHAIRMAN NELSON: Or no votes?

(No response.)

CHAIRMAN NELSON: So all voting members of the panel voted in favor of that if that is sufficient for the transcript.

Going on to the consent documents and process, there were some issues raised about the consent. Michael raised some. I know Jill and Kate and Paula and other people raised some.

So is there a condition that is emerging out of that that people think could be formulated?

MS. KNUDSON: I would like to recommend that the consent form be considerably simplified in language that the risks as listed be changed to take out "none," as we had said, to make absolutely certain that it is very clear both -- I believe Dr. Hamvas will not enroll someone who thinks there is any benefit that their baby will derive, but I would like to say it very specifically in the consent form, perhaps even in a couple of places, oh, and the

alternative, actually, that there is an alternative not to agree to be in the study.

CHAIRMAN NELSON: So let me just rephrase. So simplification of the consent language; elimination of language of risk, which we already was eliminated from a more up-to-date, but the movement of alternatives, as was previously discussed, which was also noted. And I'm sorry. The fourth was?

MS. KNUDSON: Being absolutely certain that there's no direct benefit.

CHAIRMAN NELSON: People not laboring under the misperception of benefit. Now let me ask you a specific question. One of the public comments recommended a research subject advocate. I don't know if this is funded by the GCRC or not, in which case there would be someone involved, but is that something that would be helpful or not in this context?

MS. KNUDSON: Oh, yes, I would think so, absolutely. I would love to have a research subject advocate, an outside person not associated with the research.

CHAIRMAN NELSON: Right. I assume that that such person is available at Washington University since I assumed they have a general CRC.

Why don't we focus on the consent document

itself? We can keep the advocate as a process point. But on the document itself, Michael, you had a comment about marketing.

DR. FANT: Yes. I throw this out for feedback as much as to make a point and to see what other folks may think, but in just reading through the informed consent, I think, as in any informed consent, it is just as important that the people who are signing it really understand clearly what they're signing onto and what they're not and what may be inferred and what is real.

And on the first page, -- this is under the "Parental Permission" tab briefing document -- number one, why is this study being done? To study the production of surfactant, the material that helps babies breathe but is missing in premature babies. Clear. No, no issue with that.

This is important because only about half of premature babies respond to surfactant replacement. This suggests something else unrelated to not producing enough surfactant may be causing some of the breathing problems in premature infants.

And I sort of get the sense from just hearing that, you know, just trying to put myself in the parents' position that if I enrolled my child who

doesn't have this condition, they get information, it will help them interpret the information they get from the kids who do have the condition. That's kind of what I'm kind of imagining as I think through this.

And I really think my interpretation of the comparison group is that the ability to make that connection with the kids who have RDS, it's not going to be that direct. You know, it may come at a later date when more information is known with other kids.

And I just want to be sure that however this is worded, that the parents of the kids that are in the comparison group really understand that the value of the information that is gleaned from their child may not necessarily help understand what is going on in pre-term kids at the conclusion of the study but may be important to understand surfactant biology in general and will ultimately be important. I'm not sure how to translate that into a specific --

CHAIRMAN NELSON: Well, I don't think we need a wordsmith, but the idea is to sort of de-emphasize the connection with prematurity in that that is what is being explored, but you don't want to oversell it in a way that may mislead people to think that it's a direct connection.

Jill and then Kate?

MS. FISCH: I know we're not picking this apart and taking it apart word for word, but I do agree with Michael. And I do agree with Paula. The one thing that really sticks out at me, in addition to many other things in the consent, isn't the first part where it says, "If you don't need treatment right now." That leads parents to believe that their children are receiving treatment. I'm not really sure why that is in there.

If you do not need treatment right now, you can take home an unsigned copy of this form.

CHAIRMAN NELSON: Boilerplate.

MS. FISCH: But a parent looking at that and just looking at that and maybe not reading through every word of the consent is going to look at that and say, "Treatment." You're going to focus on that word. And they're going to think their child is being treated for something. And I think that's an issue.

CHAIRMAN NELSON: What you're raising is whether that what I assume is boilerplate language in the standard --

MS. FISCH: It has to be very specific. The parents need to know what they're signing, what their children are getting into, and what the risks are. I mean, it needs to be as clear as clear can be

on a very basic level.

CHAIRMAN NELSON: Right. Kate?

MS. SHAFER: My comment is along the lines of what I asked about before, which I don't think I fully understood the response. And it has to do with the section 2 in the consent form about blood draws.

I still don't know how -- I mean, it seemed clear to me in the response earlier that the drawing of blood at times that are not consistent across patients, some of the data may be unusable and discarded or certainly not be comparable or generalizable.

So I guess it falls in a it would be nice if there could be consistency in the blood drawing so that it's done at the same time frames, rather than some kids having blood drawn five sample times over a consistent amount of time and others drawn at variable times.

CHAIRMAN NELSON: Let me ask you a question.

MS. SHAFER: It's not a condition exactly but a question.

CHAIRMAN NELSON: I understand, but as a parent, let me ask you a question. As you saw the curves that were generated from the previous work,

getting five sample points at different times gives you a nice curve. Getting two or three sample points depending upon where they fall in that curve, may or may not give you as nice a curve in that you may or may not -- hopefully would still fit on that curve but not generate as nice a curve.

There's a tension between minimizing risk by not doing additional nonclinical sampling in the absence of a catheter.

MS. SHAFER: Right.

CHAIRMAN NELSON: So you're really raising the question about whether an additional risk of a timed sample absent a catheter; therefore, a nonclinically indicated needle stick, is worth it for the scientific purpose of the investigation.

So I guess to ask you explicitly, you have asked the question twice. If you were a parent and having heard this conversation, would you say, "I'd rather have my child get an additional needle stick where I know the data is worth getting" or not?

MS. SHAFER: An additional needle stick specifically and only for the purpose of research? No.

CHAIRMAN NELSON: Correct. Well --

DR. FLEISCHMAN: Kate's argument isn't

that, Skip. Kate's argument is ineligibility criteria. If you don't have a catheter in place in which five samples can be drawn, maybe you should be ineligible because she is concerned about the quality of the data that's obtained at a haphazard moment, --

MS. SHAFER: Right, right.

DR. FLEISCHMAN: -- rather than at a --

CHAIRMAN NELSON: I understand that, Alan. That was the next place to go because I don't think it was clear. You could say just to use a needle.

MS. SHAFER: That was exactly what I meant.

CHAIRMAN NELSON: The problem there is I think the answer was given that when you get out to the two and the four-week, you don't have catheters. And so you can't get the data.

DR. FLEISCHMAN: I didn't's say I agree with that.

CHAIRMAN NELSON: Right.

DR. FLEISCHMAN: I just said that's what's being raised.

CHAIRMAN NELSON: Well, that's why I wanted to ask the prior question. So the answer, then it's just a question of you get what you get because you would not want to do an additional stick.

And in a sense, it's almost like population pharmacokinetics, instead of individual case. I mean, you end up with enough babies with the samples distributed all over the curve to where you draw a curve on average for that population of babies.

MS. SHAFER: But will there be enough babies to get that?

CHAIRMAN NELSON: That again goes back to the same question of the heterogeneity of the population. Until you do it, you don't know. But it's the same kind of tension between population PK in a sense and individual patient data where you draw a lot of samples versus a couple of samples and then get a larger population. I don't know if there's data to know. Maybe there is.

MS. FISCH: I just want to be clear on something. With the five blood draws with the catheter versus taking blood draws during the day, it's possible that that data would be unusable. So the babies would get stuck.

And it may not be useable data anyway. Is that right? I just want to make sure I'm thinking about it the right way.

MS. SHAFER: They would be stuck anyway for --

MS. FISCH: Right, right.

MS. SHAFER: The additional blood that's drawn --

MS. FISCH: Right.

MS. SHAFER: -- for research purposes may not be useable.

MS. FISCH: So they would be getting the blood draw anyway, no matter what?

CHAIRMAN NELSON: Yes.

MS. FISCH: And it would just be a matter of taking a little bit extra?

CHAIRMAN NELSON: Yes.

MS. FISCH: Okay. I just wanted to be clear on that. Thank you.

DR. MURPHY: Skip, I'm trying to see if we can help answer the question. And I think your analogy to population PK might be very helpful because in doing drug levels in general, we like to have, you know, samples every few minutes so we get these really nice curves. And that gives you the best curve that you can get.

But over time, people have developed a different approach because of all of the sampling issues. This is just in another arena where you can get random samples, if you will, but I think it comes

to your question, really, if you do it that way, then you've got to have enough numbers of the random sample. So I think that that is the question that I think you're really asking.

It's not that it's -- it would be useless if you didn't get enough samples if it turned out that way, but there are approaches that try to integrate that sort of population approach, instead of all of those time samples.

CHAIRMAN NELSON: Perhaps I could formulate a question and, with the Committee's permission, ask Dr. Hamvas to respond. I mean, we have an n of 53 that had been done previously. And I don't know if that includes the premature group in this study, but of that, there were some done at four weeks, where they probably didn't have catheters.

So is there an estimate of the number of infants whose data ultimately were not useable who were placed at the risk of the infusion but, yet, you couldn't use the data simply because of the sampling problem that we have been discussing? Is that a real problem or is that mainly just a theoretical concern?

DR. HAMVAS: So of those 53 babies or so, there were maybe 3 babies for whom we could not obtain adequate data. Two of those babies were extubated

within 24 to 48 hours of starting the study. So we just didn't have enough time points.

I'm trying to remember what the third one was. I think because of a change in the clinical condition, the infusion was stopped midway through. And so we discarded that, those data.

We have amassed a reasonable experience from getting these blood samples on babies. So we have a general idea as to what population mean and standard deviation are for these plasma samples.

So that helps us interpret if we have a baby for whom we only have one or two blood samples and one seems way out of line. It helps us understand, well, perhaps that's an aberrant sample and there was something wrong with that.

We have still utilized, then, the population mean from our plasma sampling so we can still get adequate data from those babies. So that has not been a limitation to this point.

MS. SHAFER: And that was all in pre-term, in studies of pre-term babies?

DR. HAMVAS: Right.

MS. SHAFER: So I guess the question, then, is with ten normal comparison infants, is that enough to be able to generate a picture of what those

one or two or three blood draws mean?

DR. HAMVAS: Yes. And I don't know the answer to that right now. Until we start obtaining some of the information, seeing what the spread of the data looks like, I really don't have any basis with which to answer that.

CHAIRMAN NELSON: Well, let me ask a question, then. Given that, I mean, one could formulate a recommendation that the early experience be gained with infants with an in-dwelling catheter.

In order to generate that data, you could then sit intermittent sampling if we chose to go there. I mean, that would be the direction that one could take to address your concerns.

DR. CHESNEY: I was just going to ask the neonatologists and critical care people here, how often do you have an infant intubated and not have an in-dwelling catheter for ready access? I can't imagine that happens very often.

CHAIRMAN NELSON: As a full-term, it would probably be unusual. As a four-week premature, it would not be unusual, but that's not the population we're talking about here.

DR. HUDAK: Well, I think is here for the babies who are studied shortly after birth for one of

these categories, most of these babies would have a catheter because it would be, if nothing else, surgery and so forth. There would be requirements for doing that.

The issue becomes once you get out to two and four weeks, for a kid who has got, you know, minimal, you know, if any, lung disease who is intubated, first of all, there are very few of those babies that exist without lung disease at two or four weeks who are term babies. And the second thing is they would probably be very unlikely to have a catheter.

DR. CHESNEY: Unlikely to have a catheter, even though they were intubated at two to four weeks?

DR. HUDAK: Yes. I mean, you know, if you've got a term baby who is on, you know, room air on a rate of 15 and is, you know, for whatever reason, receiving a combination of feedings and TPN, you get very few labs. And you try to get the catheter out because you've got complications with catheters.

CHAIRMAN NELSON: So I guess let me ask Kate. I think this discussion certainly can edify the investigators. Is this a strong enough concern that we should add to our discussion of condition to the protocol that the early experience be generated in

infants with catheters or would that be such an impact on feasibility that we wouldn't want to go to that extent? I mean, that's the question that your mind raises.

DR. HUDAK: Skip, I really think that the information they're going to get is on babies who have catheters who are close to birth, and they're going to get very little on babies who are two weeks, four weeks out.

That doesn't at all invalidate the question they're asking. I think the critical thing for them is to see what happens. I mean, Dr. Hamvas can speak to this, but I think shortly after birth would be adequate information.

CHAIRMAN NELSON: That's fine. So let me just summarize what I've heard about the consent document: simplification of language; elimination of language about no risk; clarification of the alternative not to be involved and putting that in an appropriate place; de-emphasis of the connection with prematurity since that is at this point somewhat speculative as, in fact, the purpose of the research; and to eliminate the template language about not needing treatment and taking it home as that that may potential reinforce the therapeutic misperception of

this study. I've left the advocate out because we can deal with that in terms of process.

So I guess that's what I've heard on the consent. Is that sufficient for our sort of high-level discussion, rather than wording?

DR. FANT: Yes. Skip?

CHAIRMAN NELSON: Michael?

DR. FANT: Just one tweak to that. Not necessarily a de-emphasis to prematurity but a de-emphasis of the data that is derived from the child to understanding what goes on with prematurity.

I think it is valid to emphasize that the data from their child will likely lead to a better understanding of a disease that has a profound effect on pre-term kids overall, but there's a bit of a leap to make the connection between their child and interpreting the data in pre-terms immediately in the immediate term.

CHAIRMAN NELSON: Angela?

MS. HOLDER: The HIPAA language, in particular, needs to be simplified and corrected.

CHAIRMAN NELSON: I agree, but I despair of a solution to that problem.

(Laughter.)

CHAIRMAN NELSON: I know. And you have

Doc Muhlbaier at Duke. So since he has written the book, I guess send them the Duke template. Do you really want me to put HIPAA in there? I mean, I can make the comment about it's -- if they simplify it down to a sixth or seventh grade level, it hopefully would then get simplified. So we'll say including the HIPAA language.

MS. HOLDER: Okay.

CHAIRMAN NELSON: Okay. So as a condition, I would like to just entertain as a condition those comments on the consent document as one condition. So do we hear a second for that?

PARTICIPANT: Second.

CHAIRMAN NELSON: I ask for a show of hands of all those in favor of the condition.

(Whereupon, there was a show of hands.)

CHAIRMAN NELSON: Any abstentions?

(Whereupon, there was a show of a hand.)

CHAIRMAN NELSON: One abstention, Dr. Fleischman. Any objections?

(No response.)

CHAIRMAN NELSON: So other than Dr. Fleischman, who abstained, the remainder of the voting members voted in favor of that condition.

So let me now go back to the research

subject advocate or it doesn't necessarily have to be that person but the notion of an advocate for this consent process and what we think about that. Dr. Hamvas gave quite a description, I think, in answer to one of Jill's questions about the consent process.

So my question is, what are your feelings about the description? And the things that should be put in place, was that an adequate description?

MS. FISCH: I think it was adequate in that you do develop a relationship with your bedside nurse, as you described, but let's not forget people go on vacation, shifts change, and you have a rotation of people on a daily basis.

I think it would be more helpful, in addition to that, to have a particular person assigned to go to with questions. In addition, I mean, the nurse is a wonderful thing to have, but I think a specific person really needs to be on board for questions, concerns, and the like, in addition to the nurse.

CHAIRMAN NELSON: Mark?

DR. HUDAK: Jill, can I just ask you to clarify for me because this is a major change in how research consent would be obtained. What is it about this particular protocol that makes you say that that

is something that we need to have as a condition? And what would limit that? What I'm saying is, you know, is this something that you think should be done for all research --

MS. FISCH: I do.

DR. HUDAK: -- or is this something specific --

MS. FISCH: Yes, I do.

DR. HUDAK: Because I think we need to be addressing things that are specific to this protocol.

MS. FISCH: Well, I would feel that way about any protocol. I mean, I think as a parent -- and I deal a lot with families who -- you know, all different levels of education, income, and so forth.

And I think no matter where you are, it's very important, you know, especially with research, that the families have an advocate or somebody to go to, be it the social worker or somebody else, to go to with their questions and concerns, you know, not just the doctors. The doctors can be very intimidating. These are the doctors who may be taking care of your child, in addition to doing this. And I think that can be very intimidating as the parent.

A lot of times I speak to families and they're afraid to even speak up to their doctors

because they're afraid their child won't get the proper treatment or they'll be looked upon poorly. They don't want to ask too many questions because they don't want to appear unintelligent.

And I think that if you have somebody else who is accessible in any research project but in definitely this one to make sure that everything is explained, I think it is very important. And I would consider it to be a condition that would --

DR. HUDAK: Well, I don't disagree with you about the process. I think that's a very appropriate way to sort of handle some of the issues we see with these things.

But I'm just wondering within the purview of this Committee in responding to this particular protocol, whether or not that is something the Committee can impose. I don't know.

MS. FISCH: Well, whether they can or can't, I mean, that's how I look at it.

DR. MARSHALL: Can I ask a question for clarification?

CHAIRMAN NELSON: Mary Faith?

DR. MARSHALL: Jill, I just want to make sure I'm understanding what you're advocating for, and that is a person, perhaps a research subject advocate,

a social worker, someone, not necessarily to oversee every consent process but someone to be there for parents to ask questions of during the process as it unfolds but someone besides the people who are already listed on that list who might feel more comfortable with the work who is available 24 hours a day, that sort of thing.

MS. FISCH: Right. All the people they are talking about, the nurses and doctors and so forth, these are all people taking care of your baby.

DR. MARSHALL: Right, right.

MS. FISCH: And I think it's really hard to sit there, you know --

DR. MARSHALL: An objective third party sort of person.

MS. FISCH: -- while your child is intubated and say, "Oh, you know, by the way, about the research project."

DR. MARSHALL: Right.

MS. FISCH: And, you know, I'm concerned about this.

DR. MARSHALL: Okay.

MS. FISCH: And there's another person to call who is removed from all of that who you can go to and even act as a go-between, you know, help you with

the consent if you don't understand. Somebody may feel more comfortable asking a question of you about the consent itself if you don't feel comfortable asking the physician.

And you will find parents who will never ask a question of a physician. They'll never question them ever. They'll just take their word, and that's it.

DR. MARSHALL: Thank you. I just want to make sure that --

MS. FISCH: Yes. Thank you.

CHAIRMAN NELSON: Paula? And then Ron.

MS. KNUDSON: Well, I actually would like this to be someone who would see the family before they actually sign the consent form to really be sure as this independent person that the family really understands and then go ahead and sign the consent form if they really aren't comfortable, that all the questions have been asked, that there is really some basic understanding.

I'm not talking about really understanding the science but understanding what their baby will actually go through and that it is indeed not treatment.

CHAIRMAN NELSON: Ron?

DR. RUBENSTEIN: So I agree also with everything that you say. I also agree with what Mark says because from a practical standpoint, this becomes an incredibly high standard for every -- if we mandate this for this study -- and you said yourself you would feel this way at any study at this review level. This is something that has to be considered in the broader context of what is it going to do to research in children in general because the resources to have somebody like this currently are not there.

So my specific question is NICUs have lots of social workers. And the social worker in the NICU being identified as somebody who could be at access, would that be sufficient? There the resource already exists.

MS. FISCH: That's pretty much what I mean. I mean, to have somebody dedicated, take a social worker who is already there dedicated to this research project.

DR. RUBENSTEIN: But they won't be dedicated to this research project.

MS. FISCH: No. But I'm saying if people have questions, --

DR. RUBENSTEIN: Right.

MS. FISCH: -- that's who they could go

to. And that would be their person if it's not for the whole project, but it could be their social worker, somebody they could go to if they're not already working with a social worker but somebody who really understands the project. I mean, all the social workers then would have to understand the project itself.

DR. RUBENSTEIN: That's putting a pretty high burden and a high demand on somebody's job. I mean, I'm not trying to take up --

MS. FISCH: No. I understand what you're saying, but I feel that the children are worth it.

DR. RUBENSTEIN: I'm not trying to play devil's advocate because --

MS. FISCH: And they need to be watched for.

DR. RUBENSTEIN: Yes. In my own practice, primarily in cystic fibrosis, we find out incredible things from the social workers that the patients would never tell us. And I'm very sensitive to what you're saying, but from a practical standpoint, you know, these are precious resources that we have in an era of tightening resources to do these studies.

I'm trying personally to find the balance. And the best way to find the balance is to create a

use of the resources that we have, but to then try to get a social worker to understand the science of this, that's difficult. And that puts a lot of demand on their time when they have other things. You know, they will all tell you that they have too much to do as well, and they're right.

CHAIRMAN NELSON: Mark, did you want to jump in?

DR. SHORT: Skip, I might just say something on that. I hear what you are saying, and I agree with you. We actually have a parent advocate that we're lucky enough to have that's funded through the March of Dimes right now.

Unfortunately, we don't control the social worker's job description. They aren't under our budget. So I couldn't go to my hospital and say I want my social worker now to understand this protocol and to meet with parents. I think they would do it on their own, but you couldn't mandate the St. Louis Hospital to say the social worker has to do this.

I think if we feel it's an important person, we have to leave flexibility within the group to pick who that person will --

MS. FISCH: It could be anybody.

DR. SHORT: Right, absolutely.

CHAIRMAN NELSON: Let me separate out function from who. Okay? And then we can talk about function and then decide who could do it. But I have heard and I think Paula had given the clear the statement of function is that someone who can at least address whether or not the parents understand what we have talked about as far as the lack of benefit and the data that is resulting. That's a particular function.

Whether it's a research subject advocate who is hired by the GCRC or the social worker or a parent advocate who is available to the unit, this may be less important.

So why don't we try and answer the question in our own minds about whether we think that function ought to be here in this study per se, even though I agree it would be great for all studies, but in this study per se whether we think that function ought to be built in as a condition.

I guess to Alan and Mark, you had your hands up. Feel free to answer a different question, but --

DR. HUDAK: Well, I guess I would say that I agree with you. In a perfect world, that would be wonderful to have that happen, but I think in terms of

the approval of this study, I can't say that we need to have that as a necessary condition.

And with respect to all studies, you know, my fears are that if you are working in a research-intensive nursery, where there may be many studies going on, different areas of study, you would have to have a number of people trained up to understand those different areas. And they have intelligent conversations.

And my fear is that if you made that a mandate everywhere, you would actually compromise research because you wouldn't be able to provide the resources to meet that criteria.

And, furthermore, there are some studies that are very, very windows of time. And sometimes we have to get babies in within six hours after birth for things. And I'll tell you, at 2:00 in the morning, you're not going to be able to have that happen.

It's difficult enough with the resources you have, with the doctors and nurses and so forth, to get that to happen. And so I just think there are some practical issues.

CHAIRMAN NELSON: I would like us, though, to just answer the simpler question of whether we should do that for this study or not, which doesn't

happen at 2:00 in the morning.

Alan? And then we'll go to Kate and Jill.

DR. FLEISCHMAN: I think this would be a fine optional recommendation, rather than a mandatory recommendation. The justification ought not be that the families are vulnerable, but the justification comes under Paula's I think rubric of since there is no prospect of direct benefit, a high risk of therapeutic misconception because we're at the 407 table, that the families be helped to understand this is a fundamental physiology study. So it would be a good idea if there were others involved in that. But I would oppose it being a mandated recommendation for all of the reasons that we have raised here.

I have done lots of clinical research and realize that these babies are very vulnerable and that these families are very vulnerable, but I don't think that stops us from being able to do a good job of getting true informed and voluntary consent, but here the justification is I think there is no prospect to direct benefit and a high likelihood of a therapeutic misconception. And we could, therefore, argue that this would be a good thing.

CHAIRMAN NELSON: Kate? And then Jill.

MS. SHAFER: As a clinical social worker

who has worked in research hospitals for many years, I would love nothing more than to mandate that there be a social worker involved in every consent process with every parent, particularly in pediatrics, but I know that the reality is that that is never going to happen.

And I don't think that this research presents a higher bar for having an identified person than many other research projects have. I think as an alternative, it might be helpful to think in terms of a re-consenting process, a revisiting of the consent with a parent certainly before the two-week re-draw or re-testing, you know, each interval to make sure that there have not been questions that come up in the interim time. And that's a fairly good way of getting parents to identify questions that they have and to understand some misconceptions that they may have had originally, so to go through a process of re-consenting.

CHAIRMAN NELSON: Before going to Jill's comment, what I thought I heard presented was that, in fact, that is what is done is that the second week and fourth week are not bundled with the zero week.

One way of perhaps institutionalizing that is to make the reference in the consent document to

subsequent testing to actually say that that will be another opportunity to consent or to not consent.

DR. HUDAK: And it says that.

CHAIRMAN NELSON: Does it say that specifically? So that was my impression that that is what, in fact, they are doing from the discussion.

Let me go to Jill.

MS. FISCH: Well, I just wanted to reiterate. I mean, in addition to my being concerned about the families being vulnerable, I probably wasn't clear. And I do share the same feelings as Paula.

I probably would have felt more comfortable had the consent been written differently to begin with. But when I first got this at home and I opened it up and I looked at it, which I won't do now, I mean, I picked it apart.

And I really feel that, as I said before, parents looking at this are I'm not going to say misled, but when you first see, as I said, "treatment," that's why I feel it really is important once it's rewritten who will look at it again to make sure that it's within the standards that it should be where parents will understand.

Can we add another phone number in addition to the physicians listed of at least the

social work department to call if they have questions? Maybe they don't have that number accessible. And it could be on the consent form. Is that a possibility? Because right now there's nobody else listed to call with any questions.

CHAIRMAN NELSON: Often the IRB is listed, is it not? It is. But that may be not be written in a warm and fuzzy "Approach us" kind of way.

I guess whether it's social work, the broader question is access for the parents to raise questions that might not be answered by the individuals at the bedside and other clinical care or research.

MS. FISCH: Right.

CHAIRMAN NELSON: Whether it's the social work department I guess is less --

MS. FISCH: Whomever it is.

CHAIRMAN NELSON: Yes.

MS. FISCH: Whoever they decide for it to be.

CHAIRMAN NELSON: That could be maybe change. I don't know exactly how it's worded but making that a more approachable way. For example, in our institution, we change that from the office to the individual because who is going to call an office its

name, "the Office of Human Subject Regulation"? No one is going to call that office in their right mind, but they might call a person who has got their name listed there.

MS. FISCH: Right.

CHAIRMAN NELSON: So we could certainly do that. Let me ask you a question with this discussion. I mean, I think the issue before us, everybody agrees that this is a good thing to have. I hear a lot of disagreement about whether it should be a condition of approval or a recommendation.

I'm happy to put it to a vote as a mandatory condition if you feel strongly and will ask people to indicate whether it should be optional or not or if optional is fine, we can just stop there.

So I guess I'm happy to go either way. It depends on in order to bring the discussion somewhat to a close on the point.

MS. FISCH: I would say for it to be optional, but I would be I guess more comfortable with somebody reviewing this with the family before they sign it other than the physicians doing the research and just make sure they understand.

CHAIRMAN NELSON: Okay. But as an optional recommendation?

MS. FISCH: Right.

CHAIRMAN NELSON: I think that's fine. Anyone have a disagreement with that. Paula?

MS. KNUDSON: Yes, I do. I'm sorry. I know it's an imperfect world. I know it's a terrible way to have to do research, but I'm terribly concerned about the families. And I really think that it should be mandatory that there is a third party who speaks with them and offers them the assistance of being at least the liaison to get the questions answered who may not be able to answer the questions themselves but can be the person to send them to the right person for the answers.

CHAIRMAN NELSON: Well, I'll take that as a motion and then ask for a second.

DR. MARSHALL: Second.

CHAIRMAN NELSON: So the motion is made and seconded that this advocate -- and we haven't specified who; we'll leave that open -- but that the function of an advocate specifically during the process of consent prior to signature be added to this protocol, not to all research but to this protocol, for the purpose of reviewing particularly the lack of direct benefit, the physiologic nature of the protocol, and to reinforce that there is, in fact, no

therapeutic benefit to the parents' individual infant.

So I guess I'll ask for hands of all of those in favor of that as a mandatory condition.

(Whereupon, there was a show of hands.)

CHAIRMAN NELSON: I saw it done two different ways the past two weeks. I'm happy to read the names so you have it orally in the record if you keep your hands up. So Jill Fisch, Paula Knudson, and Mary Faith Marshall all voted in favor.

All those against it as mandatory?

(Whereupon, there was a show of hands.)

CHAIRMAN NELSON: Kate Shafer, Angela Holder, Ron Rubenstein, Alan Fleischman, Mark Hudak, Joan Chesney, Michael Fant, and Billie Lou Short.

DR. JOHANNESSEN: How about yourself?

CHAIRMAN NELSON: I thought the Chair only votes when it's a tie.

DR. JOHANNESSEN: Okay.

(Laughter.)

CHAIRMAN NELSON: I get to wiggle out.

Michael?

DR. FANT: Yes. This is one of those questions obviously that, you know, there is sentiment on agreement to some degree by everyone, I think, but there is some conflict in terms of how to implement

it.

You know, I voted against mandatory implementation for this protocol for a couple of reasons, not because I don't think the function of the advocate, you know, the functional endpoint of having the advocate is not critically important, especially for this comparison group in this study.

So I think ensuring all of that understanding that the family has, getting their questions answered, I think that is essential and very important for this protocol. But I have trouble feeling confident that an ill-defined person who is employed by an ill-defined employer, who has ill-defined links and linkages within the university is going to be viewed or function any differently than well-intentioned investigators. And it would, in essence, add an extra layer of burden onto implementing the study and getting it done and may even result in some declines in enrollment unnecessarily.

So I'm more concerned about the functional endpoint that we all I think are talking about. I think there's a lot of uncertainty in this ill-defined person and who they are or how they are associated with other folks because I'll tell you, when I think

of people in my own family and friends who go to the hospital, anybody who is employed in that building on the same team, they're all together. So they aren't distinguishing between a social worker or a doctor or a nurse or an administrator, you know. They're all on the same team.

And I'm not sure how that would work in practical terms to achieve the things that I think you're pointing to.

CHAIRMAN NELSON: Mary Faith?

DR. MARSHALL: I guess I am just going to make the argument that we have heard from a family member and a family representative who sees through a different lens than most of us at this table. I think even differently than your lens.

And I think that what we have heard is an argument for someone to be available, not someone to have to be there 100 percent of the time but someone to be available when desired and when needed.

And we have heard the perspective, Jill's perspective, who has told us -- and we know this -- that families maybe are afraid to ask investigators or they're afraid that they're going to look stupid. And her reality is just as valid and real as ours is and I would say more so from her perspective.

And I think the onus should be on us if we are going to pay verbal homage to the idea that informed -- and I'm emphasizing "informed" -- consent is important. And if we're hearing that the family members would like to merely have available -- this person doesn't have to be there every time; a name and a phone number on a piece of paper I think is what you are asking for -- that I guess I would argue that the onus is on us to believe what Jill has to say, rather than for us to say we're not sure or don't understand whether that would meet the need.

I think she probably has a better perspective than we do on whether that would meet the need.

MS. FISCH: Thank you.

CHAIRMAN NELSON: Well, I might point out that, actually, that is a different modification to say that you just need an approachable name and telephone number to the consent document.

DR. MARSHALL: That's what I was understanding she was saying.

CHAIRMAN NELSON: I understand. That's not what the motion was, nor what Paula wanted. So that's why I'm trying to be very concrete.

DR. MARSHALL: Okay. Sorry.

CHAIRMAN NELSON: And I'm more than happy to incorporate into the previous thing about the consent document the approachability of the name and telephone number that's available to meet that if that's fine with whoever made that in the first place as a friendly amendment to that one.

DR. MARSHALL: Thank you.

CHAIRMAN NELSON: I think Michael gives voice to the ambivalence. I mean, yes or no seems black and white. This isn't black and white.

We are scheduled for a break at 3:00 o'clock. Let me just ask one question before we just take a brief break because what I will do after the break is try and summarize where we are and then see where we need to go to sort of finish up.

The question is this -- and if it needs more discussion, we can deal with it after the break -- that this protocol came to us as a sequential protocol. It came to us specifically over the inclusion of the comparison group. The research is ongoing and had been ongoing about the premature group to which this data is being compared.

So the question is whether or not we as a group want to either reaffirm or change the assessment of the local IRB or give comment on the assessment of

the local IRB about the approvability category of that particular research, which was placed under 406 or 50.53.

Mark?

DR. HUDAK: I would say we weren't asked to do that. And I would not want to make that the purview of this Committee.

CHAIRMAN NELSON: So I take that as a motion no, we don't want to comment on that assignability.

DR. CHESNEY: I second the motion.

CHAIRMAN NELSON: All right. So I guess the question is, all in favor of -- Alan, discussion?

DR. FLEISCHMAN: I can understand why not. I would ask Mark and Joan to help me understand what the risk is of our doing that. And I would also like to ask the Chair, why did he ask the question? I mean, I'm trying to understand why we shouldn't go where he asked us.

CHAIRMAN NELSON: I'll answer the first easily. I was asked to ask the question. I'm happy with people saying they're comfortable. I'm assuming a vote to say we're not going to comment is sort of an implicit endorsement of that, but that is a whole separate issue.

Ron?

DR. RUBENSTEIN: I think that that responsibility has been delegated by statute to the local IRB. The local IRB has executed their judgment and statute.

There is not really a role for the Advisory Committee in that judgment. We're not being asked to consider it. And there's not statutory reason for an advisory committee to oversee that.

If there are problems with the local IRB, that's something for OHRP and FDA to deal with. It's not the jurisdiction of this Committee, I don't believe.

CHAIRMAN NELSON: Anybody have a problem with that?

(No response.)

CHAIRMAN NELSON: I mean, that's not really a motion. It's just a point of discussion. And so hearing no motion on that, I guess let's take our break.

We'll start again at 3:15.

(Whereupon, the foregoing matter went off the record at 3:01 p.m. and went back on the record at 3:20 p.m.)

CHAIRMAN NELSON: Well, let me make a

couple of comments and then summarize our discussion. I think the first comment is I was asked a question I would state broadly as sort of process. I mean, once we finish here, what happens? Let me just make a couple of quick comments about that.

At the end of the day today, we should all leave the room with a very concrete idea of what we've recommended and the various conditions that are attached to that recommendation.

What I will then do is write that down in a way that would then be presented concretely to the Pediatric Advisory Committee tomorrow; whereas, previously when we met together with some similar members and a lot of different people from when we reviewed last September, I had three or four days between the two committee meetings just because of the way it worked out. And so I could spend a lot of time, if you will, dressing the turkey. I mean, all of the --

(Laughter.)

CHAIRMAN NELSON: A lot of stuff I could do, all of the reasons why and all of the discussion, I mean, there's been a lot of rich material presented, many of which has answered a lot of our questions that we would have had if all we had was the paperwork, for

example, in the presentations this morning.

Since I have to do this between today and tomorrow, I'm not going to have the time to sort of lay that out. In many ways, I see this as similar to the FDA's sort of rulemaking and commentary process. There's going to be the rules, in a sense what we have recommended. And then there's all the commentary that you can construct around that.

That commentary, although of interest, is not going to be as rich, if it's even there at all, between today and tomorrow. So you should know exactly what that is going to look like.

Now, once that is reviewed and the Pediatric Advisory Committee takes final action on it, I might say to reassure you at least at the last process there were two additional recommendations that they added, which I would characterize as fairly minor. But they could do anything they want basically. And we'll see what happens.

Then those go up through the process to the Commissioner and to the Secretary that has been outlined previously. And then the local institution works with OHRP and the FDA to sort of meet those. And there are plenty of people in those offices to review that process.

So I guess what I am saying is there needs to be a certain amount of faith in the process that when we give our recommendations, that they can, in fact, be executed to where it is possible to say, "Please simplify the language" without necessarily getting into a chapter and verse kind of discussion of the language that needs to be simplified.

So having said that, what I would like to do is just go through and summarize our previous discussion and see if there are any other conditions we want to put on the table and then once we do that, go back to the original motion, if you recall, which was for approval with conditions under 45 CFR 46.407 and 21 CFR 50.54. So we'll then go back to that as the motion.

So the conditions I have are two required conditions and one recommended or optional conditions. The first required condition is a careful look at the homogeneity of the comparison group in order to assure that the comparison to the premature data is meaningful.

And examples, which does require a certain amount of expertise, were cardiac lesions affecting lung flow as well as hypoplastic lungs. But the recommendation I think will be written at a general

enough level that we don't have to assume that all of us around the table necessarily have the scientific expertise but that we say that that group should be homogenous enough to make a meaningful comparison to the data about the premature infants that has already been collected.

The second is related to the consent document itself. And there are six recommendations there. First is simplification of the language, including the language that is there for the HIPAA requirements. The second is that language referring to no risk be eliminated. The third is that the alternative section clearly indicate that one alternative is not to be involved in reframing that question from the perspective of participants and not investigators.

To reframe the question of the connection of the data derived from these full-term infants with prematurity so it's understood by the parents that that is somewhat tentative and that the connection there is not as direct as it may appear from how it is currently worded, that the "not need treatment" language be eliminated given that that might reinforce the therapeutic misconception, and that under the area that discusses individuals to contact, that that be

framed in a way that there can be an approachable avenue for contact, which in my mind is someone who has a first and last name with no fancy degrees attached to it, so that parents can think there is someone they can call who would be an approachable advocate for them in answering questions surrounding the trial, which probably is not the chair of the IRB, probably not the regulatory office; so however that is worded, just paying attention to that.

The optional one was the discussion we had about someone who is actually present and available during the consent process to reinforce and assure themselves that the parents are not laboring under sort of a therapeutic misconception and understand the exploratory and physiologic nature of this particular research.

We don't have to rehash that discussion, but given the discussion that we had, the feeling was that we couldn't be concrete enough about that to where we wanted to make that a mandatory recommendation. But, yet, that would be under an optional category of highly recommended but not required.

So that is what I have heard and what the list would reflect. So I guess before going back to

the primary motion, which was approvable with these two required conditions and I guess the optional one as part of that package, let me see if there are other things that people feel should be put on the table into these categories.

(No response.)

CHAIRMAN NELSON: So I guess, hearing none, I don't recall who made the first motion, but I guess the motion was approvable with these conditions under 21 CFR 50.54 or 45 CFR 46.407.

So I guess all in favor of that particular motion, raise your hands?

(Whereupon, there was a show of hands.)

CHAIRMAN NELSON: Any abstentions?

(No response.)

CHAIRMAN NELSON: Any rejections?

(No response.)

CHAIRMAN NELSON: So the record could show that the vote was unanimous of all voting members of the Committee. Do I need to read the names?

DR. JOHANNESSEN: No.

CHAIRMAN NELSON: Thank you.

Now, I'm sure there are some clarifying things that we'll need to continue to clear up, but since we've voted on that motion that seems to be

there, let me just say at least how I understand if we begin to frame the bigger picture, how this came to us and the like, and see if there are any modifications of that on the part of members of the Committee.

To a large extent, what we had been asked to review here or what we are reviewing is an amendment to an existing protocol. The amendment was to include a comparison group in a protocol that to date appears to be largely completed but may still have a few infants that need to be enrolled looking at surfactant physiology in pre-term infants at three different post-gestational ages.

That prior protocol was reviewed and approved by the IRB under 45 CFR 46.406. And they probably didn't include the FDA language because they may not have realized it was also under 50.53, which is the same minor increase of a minimal risk, no prospect of direct benefit, and the premature infants having a condition.

Although we see no particular reason to comment explicitly on that, I think it's important to emphasize that our review of the amendment obviously needs to take into account the whole context of the protocol and that if we had wanted to comment, we certainly could have commented if we so chose, just to

make clear that that's the case.

But I don't see any particular reason in the written record that I'll produce to the Pediatric Advisory Committee to really say anything more than that. Is that fair? Alan?

DR. FLEISCHMAN: Skip, I think it would be helpful in the written record for the Committee and the public to understand that we're reviewing this because of a technicality in the extant regulatory structure; i.e., the definition of condition and the complexity of this 406 category.

It seems to me that when the National Commission recommended having this 407 category, it was conceiving of things far more risky than what we're discussing today. It was conceiving of things far more momentous than the need to do what seems to be a fairly low-risk physiology, biochemistry, exploratory study.

And it would be unfortunate if the public or the media felt that this was risky business on very sick small babies. This is not risky business, but because of the regulatory structure that we have and the definitions that we have, it's appropriately come to this forum.

I really think it's helpful to have that

in the record. And that's why I thought it was a good idea to point out that they did approve the prior work under 406 and that they felt they could not based particularly on the definition of condition.

CHAIRMAN NELSON: I think that's fine, Alan. And we could spend a few minutes sort of talking more generally outside of this particular protocol.

One of the issues that I think has been implicit in our discussion that I will make explicit is that the protocol be conducted according to sound ethical design. And I think it is.

But there is in the literature even a discussion among those looking at research ethics about whether or not this minor increase over minimal risk is the appropriate degree of risk confined to a narrow range of interpretation by a conservative view of minimal risk for all children independent of the condition to be exposed to.

You know, you know those references. I do. But there is a feeling. Our regulations do not allow that because of the tieing to minor increase over minimum risk to condition, as you pointed out.

So I think from an ethical perspective, assuming a conservative definition of minimal risk,

which, granted, there is some variability, but assuming that, I personally don't have any problem extending that same risk category on ethical grounds to children that do not have a narrowly defined condition given our previous discussion, so that as a sort of general comment, but that's out there in the literature but not available under our current regulatory structure. Is that fair?

DR. FLEISCHMAN: Yes.

CHAIRMAN NELSON: So let me ask, are there other issues that we haven't addressed? You're going to have to drag it out if they're not. Are there other issues that we have not addressed that we need to address to make sure that we have done our job.

DR. MURPHY: We've done risk. We've done benefit. We've done category. We've done mandatory. We've done optional. We've explained. I guess that from FDA's perspective, we don't have any more questions for OHRP. Bern, do you all have?

DR. SCHWETZ: No, I don't have any additional questions.

CHAIRMAN NELSON: You mean, we could actually end early? I don't know if I have ever been in an FDA meeting that has ended early. I'm feeling terribly disoriented.

(Laughter.)

DR. MURPHY: Well, we have two more days.

CHAIRMAN NELSON: All right. Well, I think we could use our time. And I think it would be productive to just go around the room briefly. I would be interested in hearing people's sort of reflections on whatever you choose to say relative to our process today. And if you don't have anything to say, feel free to pass. And then we can adjourn at that point.

Why don't we start over here? So I'll give Jill and Kate the last word. Billie?

DR. SHORT: Yes. I think it's been actually a very good process. And I think it's been focused, and it's excellent to have the multi-disciplinary group here. And having parents and social workers is key on this. And so I think it has been an outstanding process.

DR. FANT: I concur. Nothing really else to add.

DR. CHESNEY: As always, a tremendous learning experience. I always very much enjoy the science and understanding that better.

I am particularly intrigued by Alan's last comment that we wouldn't be here and that there

wouldn't have been nearly as much time, effort, and people power put into this if it weren't for the language.

And I guess that's one of the most important messages for me is how important a word can be in determining a huge process. And I wonder if there is room for modifying that word in some way.

DR. HUDAK: I think it has been a very good process. And I guess my only other comment is I am surprised knowing what sort of research is done that this is the second time this has come to this Committee only.

DR. FLEISCHMAN: I just want to thank you, Skip, because I think both the materials and your chairmanship have been really excellent.

DR. RUBENSTEIN: Yes. Also, as I was reflecting on this, the other time I have been involved in a 407 committee and the other studies that I know have gone to 407 committees have been far riskier, far more dangerous.

And, you know, I echo with Joan. I really would hate to have this process become very highly utilized for research that we all agreed was really a very minor increase over minimal risk.

You know, this is a lot of people power

taking away from things that we should all be doing for a day, not that it isn't valuable, not that we all didn't learn lots of things, but if there is an opportunity to try to further define what comes to one of these committees in some way I think it would be helpful.

DR. MARSHALL: Well, I want to reiterate thanks for Skip's chairmanship skills. It's almost hard to imagine having one of these without him. He's been there since almost the beginning -- and to say that I also would like to thank the presenters this morning, including the PI, because I think they made very thoughtful presentations that were well-balanced in terms of the audience. And I found them very helpful, in addition to the materials that we had ahead of time.

So it was really a well-structured day that I thought went very well.

MS. HOLDER: This is my first 407 committee. So I learned a great deal. And I think Skip did a great job. I agree with Joan that there has got to be more clarification of all of this.

MS. KNUDSON: At the risk of "me-too-ism," I will say I agree with everyone who has said that your chairmanship has been excellent. The materials

have been excellent.

I am absolutely amazed at the wonderful people who are here presenting and on the Committee. It's been a valuable experience for me. Thank you all.

MS. SHAFER: There's not much more to add. It's interesting to me, though, that for me, the science of this meeting and the regulatory processes that we've had to think about are as equally complicated. It's a challenge to understand both of them. And to put them together has been really enlightening.

MS. FISCH: Maybe I won't have that much to say now, but I agree with everyone. And I think you did a wonderful job. This is my first 407 meeting as well. I am heavily entrenched in the world of newborn screening committees statewide and so forth, and this was an incredible learning experience for me, scientifically, procedurally, the whole nine yards.

And I enjoyed meeting everybody and hearing what everybody had to say. And I appreciate everybody taking the time to license to me as I try to represent our families and children.

And I thank you all.

DR. MURPHY: Skip, could we ask Dr. Hamvas

and Dr. Frankel their perception of the process?

CHAIRMAN NELSON: Sure. Maybe they don't want to share it.

(Laughter.)

CHAIRMAN NELSON: I haven't written anything down yet.

DR. MURPHY: I just think that clearly it is a tremendous effort on their part and would like to hear from them.

DR. HAMVAS: Well, thanks for asking.

As I said, when all of this was evolving, -- I guess it was November or December -- it's turned into a very long process. So this has been going on for me for about six or seven months already.

And despite Dr. Goldkind's and Dr. Prohaska's best efforts to say that, you know, we are here to support you and everything, it is very difficult to feel supported when you are being asked for all of these documents and making sure that everything is lined up and that there are no conflicts in wording and everything.

So I must say that it was really a very intimidating process to prepare for this. I started feeling more comfortable about it until I started seeing the public comments. And then once I saw the

public comments, then I realized that I live in a very focused world and that there are a lot of other viewpoints out there.

You know, I am very sensitive to parents. And our intensive care unit is one of the models for family-centered care in the United States. However, that still doesn't give you the entire perception of other people in the world. So it's been very, very fruitful.

I think that actually seeing some of the discussion and hearing the discussion about some of these very difficult tasks, you know, trying to show that the science is reasonable is one thing.

But then, you know, everything that we know when these regulations and guidelines are developed, everything is with the best intention for providing good science but, yet, protecting people. But, yet, there are these very subtle nuances within the words that can be interpreted in so many different ways.

And, you know, it's so important to continue to make sure that we're critically evaluating everything that we do in our routine clinical care and in our research to try to take care of these babies better.

But it's also important to be able to move the science forward without being unduly harnessed or unduly burdened with regulatory things so that it's just impossible to perform any research at all.

But, again, I want to thank the Committee. I feel much better after hearing all of the discussion. And I tip my hat to all of you. Thank you.

DR. FRANKEL: Well, I'll just add that I thought this was a very enjoyable meeting. It was very informative. It is everything that we hoped it would be. It provided a lot of guidance, a lot of information that I can take back that will help in our other committee meetings and deliberations that we make there.

I found all of the discussion to be very thoughtful, very thought-provoking. And I am glad that I had an opportunity to come, meet you all, to hear your thoughts, learn about some of your experiences.

We appreciate you taking the time to help us in our deliberations with this type of protocol because I know it will help us in the future.

Thank you.

SUMMARY OF DELIBERATIONS

CHAIRMAN NELSON: Thank you. And I guess as a closing remark, the process is only as good as the people around the table and the people that have put the work into getting the materials, et cetera.

And so I thank everyone who has been involved in the process within the Office of Pediatric Therapeutics at FDA, the OHRP, and then everyone around the table, that it's only as good as the people who sit around the table and bring their ideas and experience. And so I certainly appreciate everyone's input.

So, with that, I guess we're adjourned.

(Whereupon, at 3:44 p.m., the foregoing matter was adjourned.)