FOOD AND DRUG ADMINISTRATION

84TH MEETING OF THE
CARDIOVASCULAR AND RENAL DRUGS
ADVISORY COMMITTEE

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P R O C E E D I N G S (8:35 a.m.)

Agenda Item: Call to Order

DR. PACKER: I'd like to call this 84th meeting of the Cardiovascular and Renal Drugs Advisory Committee to order. Today's session is an open discussion on inhaled nitric oxide. This is not a drug or agent to be considered for approval today. It is a general discussion of a number of issues related to its characteristics, and issues that have arisen during its development for specific indications. The committee is asked for general specific guidance about this agent, and its potential for further development.

We have with us the members of the advisory committee, and a number of temporary voting members. In the usual fashion we will just go down the committee and have everyone introduce themselves, and then go on to the temporary voting members, and have them introduce themselves.

[Introductions were made.]

DR. PACKER: Joan, do you want to read any administrative issues that need to be covered before we begin today's proceedings?

DR. STANDAERT: Yes. The following announcement addresses the issue of conflict of interest with regard to this meeting, and it is made a part of the record to preclude even the appearance of such at this meeting. Since

the issues to be discussed by the committee will not have an immediate impact on a particular product, but rather may have widespread implications with respect to entire classes of product in accordance with NTUSC 208 waivers have been granted to each member and consultant participating in the committee. A copy of these waiver statements may be obtained at the Freedom of Information Office, Room 12A30, Parklawn Building.

In the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such deliberations and their exclusion will be noted for the record.

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

DR. PACKER: Thank you, Joan.

We traditionally reserve some time at the beginning of the meeting for comment. Is there a public comment from Dr. Weinberg?

Agenda Item: Public Comment

DR. WEINBERG: As a neonatalogist in New Jersey, we are working in a non-ECMO unit, and feel that we have

treated many babies on protocol now for a year now with apparent efficacy and apparent safety, and we think have reduced the need for transport to ECMO units.

However, at the toxicology laboratory we have been concerned about possible toxicity of inhaled nitric oxide, and have examined this in animals, and I would like briefly to present some of that information.

We studied lung macrophages in mice who were exposed to nitric oxide for short periods of time, for about five hours at dose of 10, 20 and 100 ppm. What we found was when these cells were stimulated subsequently with LTS and gammainterfeuron, they were markedly primed, markedly upregulated to secrete nitrogen oxide. This is much the same effect as other pulmonary irritants like ozone might have.

This was correlated with an increased expression of INO in these cells.

Significantly -- this might be hard to see -- but B is the lungs of animals exposed to nitric oxide, and the same for NBT. That indicates that superoxide secretion by these cells as increased as well as it might be after inhalation of a pulmonary irritant.

To assess whether this might have any importance or any meaning, we stained for nitro tyrosine, which might be an effect of pyroxinitrite mediated protein alterations.

You see that it was markedly increased in C; the brown staining pointed out.

Similarly, at 40 and 100 ppm, at the higher doses, the lung lavage protein was elevated in these animals, indicating that there might be pulmonary epithelial damage as well.

So in summary, we would like to point out that this is nitric oxide being held in room air, and the effect really resembles that we've seen in our laboratory to other pulmonary irritant such as ozone. Despite what we have experiences as the lack of short-term toxicity, we would to suggest that when discussing the efficacy now, we should consider longer-term toxicity that might not be evident on the macro level for a very long time.

Thank you.

DR. PACKER: Thank you. Is there any other public comment? If not, before asking the sponsor to begin its presentation, I'm going to ask Ray Lipicky to give us an overall introduction to today's hearings.

Agenda Item: Introduction - Dr. Lipicky

DR. LIPICKY: Well, as you introduced, Dr. Packer, this is not a usual advisory committee meeting. I think it is occurring at the grace of Anita, who has been working in the area extensively, and is willing, along with all of the other investigators that contributed to what we know about

nitric oxide to airing a public discussion that has no necessary regulatory implications, to try to get the community to come together on an understanding of where things are.

From my perspective, the problem is that at one point in recent past, European regulatory agencies gravely restricted the use of nitric oxide in the clinic, because they were concerned with overall safety. In this country, people -- at least people that call me -- think that it works, and has been proven to be clinically effective.

Those are widely discrepant views. All of the information that is necessary to view is clearly not in the published literature, so that it sort of requires getting things together and presenting them, and laying things out in some kind of a pattern.

So this meeting is kind of along the lines of where is it now, and where does it go. It also is along the lines, and the last question that will be posed to the advisory committee is that we do have individual investigator investigational new drug applications. The existence of those applications in fact can be viewed as inhibitory to the ability of anyone who wants to do something that is like a large controlled clinical trial, of getting it done.

That responsibility rests entirely at our feet,

and I think that the one thing that we want you to consider today is whether we should change our attitudinal set with respect what individual investigator INDs should do, or in fact if they should even exist.

It turns out that when nitric oxide first got exposed to the agency, it was exposed to the agency as an agent that decreased pulmonary hypertension. Since our division is the blood pressure doctors, we were given the responsibility of dealing with nitric oxide. Since it was introduced as a pulmonary vasodilator, it has taken on image of next to god, and so it has changed some.

DR. PACKER: Ray, I appreciate the introduction. I guess this committee has generally seen a sponsor's presentation of data to us about solids and liquids, but this would be the first gas that we have seen for a therapeutic indication.

We'll ask Ohmeda to proceed with its presentation. Let me, in doing so, ask the sponsor that the schedule for today's presentations is a long one. The questions that have been asked for the committee and its consultants to consider are extensive, and it is absolutely essential that we remain on time, otherwise we will never get through or survive today. So I would really ask all of the presenters to at least on time, if not shorten their presentations to allow for adequate interaction and discussion with the

committee so we can get to the open discussion periods in a timely fashion.

Agenda Item: Sponsor Presentation

DR. ZAPOL: Thank you, Dr. Packer, Dr. Lipicky, and company. My name is Warren Zapol. I am an anesthesiologist from the Massachusetts General Hospital. I kind of got you into this I think in many ways. So I've got about 15 minutes to flash through why you are here from my standpoint. I won't answer the questions, which have been skillfully posed to you, but I'll set the stage.

Nitric oxide is interesting and useful, because it's a free radical. Anesthesiologists like drugs that come on and go off, and so do pediatricians. Nitric oxide has an unpaired electronic which makes it highly reactive, and makes it a very rapid signal.

It is 11 years old now. It just had a birthday party since Louis Naro(?) and Sal Moncota(?) conceived of it as the core substance of endothelium-derived action factor(?) 11 years ago.

Everything you need to know for this is on the slide. INOS makes natural nitric oxide. It's one of the three isoforms that does it from arginine, a common amino acid around house. NO is rather fat soluble, and moves very quickly, but it's not very water soluble. It's rather like oxygen, and it wouldn't do anything if it wasn't fat

soluble. But since it is fat soluble, it moves very, very quickly.

It crosses the membrane and activates soluble guanaylate cyclase, making cycled GNP, broken down by phosphodiesterase. Thanks for proving disaggregate, which will inhibit phosphodiesterase, and will be extremely useful to us.

Cyclic GMP relaxes vascular smooth muscle and inhibits leukocyte adhesion. It is a modest inhibitor of platelet adhesion and activation, which is very interesting for us to look at in new babies.

It inhibits cell proliferation. It inhibits remodeling, and is therefore extremely useful from that standpoint. There are perhaps hundreds and hundreds of papers on this now, in the nine years or so that people have been working with it.

Now we're in this section, I have a feeling, because when I came across in my IND, we were talking about NO and the most commonly used drugs of NO, sodium nitroprusside and nitroglycerin. It was the business end of those molecules. It does not require metabolism or anything when we provide it, and therefore it is useful for us.

It bind to heme and heme-containing proteins. That is its reason for targeting guanaylate cyclase and cychrone(?) P540. It converts to nitrate and nitrite. It

certainly raises the plasma level, and it ends up going out in your urine in an aqueous solution at PO2 of 100 or so. It has a half life of about six days.

In 1989, I was looking at a job in Los Angeles. I opened up the Los Angeles Times and there next to the weather report was this little report. It said that if you lived in Los Angeles, you breathed ozone, nitrogen dioxide, carbon monoxide and particles. Since I was working on nitric oxide in my lab in a cylinder with a skull and crossbones attached to the side of it, I was kind of interested in the fact that people breathe nitrogen dioxide, which is the daughter product of the oxidation of nitric oxide.

It therefore occurred to me that maybe it would be useful to breathe it therapeutically. So when I got home, I called down to North Carolina to NIOSH and I asked them what were the limits on breathing nitric oxide? They said it's not really very toxic. You can breathe it eight hours a day at the workplace, and the limits there are 25 ppm per 8 hour a day working exposure. That was very helpful for me. It allowed me to use it in my lab, and it allowed me to give it to babies in 1989.

So here was the dream, and this is the dream that you will talk about a lot today. We believed that if arginine was being converts to NO and NO was conically

activating guanaylate cyclase and making cyclase DNT, that these cells might be out of balance with the number of smooth muscle cells and/or these cells might be injured by endotoxin or other things that injure the pulmonary circulation.

Wouldn't it be neat if we could supplement the amount of NOV cells made by inhaling some? Yet we would go, we hoped, one step further in a very important step. We didn't want to cause systemic vasodilation. Because I'm an anesthesiologist, I had killed a number of people by giving them intravenous vasodilator substances. You only have to do this once or twice in your life, you will set it in your sights for a labor.

We hoped that the NO would go across and combine very rapidly with the hemoglobin 10,000 or 20,000 times faster than carbon monoxide does and inactivate itself, and therefore it would not circulate, and would cause system vasodilation.

We perform a nitric oxide(?) heme which would go to med heme, an electron with peer from somewhere so that it would create the met fere(?) heme to ferrous heme and recycle. It's a natural substance. I presume this is one of the reasons your cells can handle it, and deal with it, and work that way.

We had a problem. How could I get it? Some

people in England had been measuring ELNO. They had mixed NO in bags, and breathed from the bags, and measured the diffusing capacity of nitric oxide. I knew that I didn't want to make NO_2, which in water makes nitric acid, which makes acid rain, which is bad. I knew that I had to take the NO and store it in nitrogen, and then mix it with air/oxygen immediately before inhaling; scavenge NO_2 and some NO with soda lime to keep it down, and measure what I was doing.

A simple experiment. If you mix 20 ppm nitric oxide and 91 percent oxygen, it will about half convert in about 30 minutes to nitrogen dioxide. We consider bad EPA levels at 1/10th or less of NO, and therefore we knew we had to stay out of the NO_2 business if possible.

So in 1989, we took a sheep. We opened the windows in the lab. We all wore gas masks. We took the sheep. We put Swann-Gantz catheter in it. We tightened up its pulmonary circulation, and we leaked in some nitric oxide to the sheep's breathing basically in the first study published.

It was quite obvious what we did. We tightened up the pulmonary circulation, breathed 80 ppm nitric oxide. We got a vasodilation. We restricted the sheep's pulmonary circulation, but more importantly we found no change to systemic arterial pressure. In the thousands of humans that

have been studied since then, nobody has convincingly shown me hypotension in the systemic circulation by breathing NO.

We showed at the same that even 5 or 10 ppm could produce a reversible dilation of the pulmonary circulation. Interestingly enough, it only lasted for about as long as you gave it. If you gave it seven minutes, and it was gone in two to three minutes. If you gave it for seven minutes at 10 ppm, it was gone in two or three minutes.

Below that wonderful EPA number of 25 ppm, we could get nice physiological effects, and therefore we were quite happy. Jay Roberts, who I convinced to help me with this study got interested. We started to think about all kinds of applications.

Prouse(?) was a fellow in my lab at the time. He went home to Sweden, and like all of my fellows, he put a Swann-Gantz catheter in himself and breathed 12 percent oxygen, tightened up his pulmonary circulation, and here it at one minute and two minutes breathing 10 ppm nitric oxide. His PA pressure when down to the baseline level. So now we knew not only did it dilate constrictors in sheep, but it reversed human hypoxic pulmonary vasoconstriction, a common enough phenomenon, responsible for lung deficiency.

Now Patrick(?), who was in the lab with me at the same time, went home. He said his grandmother had known for years that nitric oxide was a great pulmonary dilator,

because all over Europe people had sold these anti-asthmatic cigarettes for asthma and oppression, respiratoires. They were actually sold in America. You can find them in all the old dictionaries in America, a medical formulary in America.

Here is Patrick. He put a Swann-Gantz catheter in himself, made himself hypoxic, breathed 11 percent oxygen, got his PA pressure up to 40. Now here he is breathing a gauloises(?), a French cigarette, and you can see his PA pressure coming down to about 20. He smokes the gauloises. When he stops smoking the gauloises back up it goes. He gets a little hyper reactive.

So we smoke. We drop our PA pressures with a smoke. We do a couple of terrible things with smoke. I'm just saying that that one component of smoke -- this is quite common -- humans treat themselves with it all the time. I suppose that when you cart your load up Everest, the reason the Sherpas sit there on the rock smoking is they drop their PA pressure.

Now I started my life intellectually in this building. I spent three and a half years in this building doing ECMO before many of you were born. I worked with the father of ECMO, a fellow by the name of Ted Kolobow. I spent 11 years of my life working on ECMO machines. These are the same machines that are used today. They are in slightly different configuration.

We wound these ourselves. We started by profusing fetuses by arterial venous profusion, which is an invasive technique. It destroys platelets and it is difficult. It requires anti-coagulation, but it's perfectly effective, like dialysis of electrolyte I assure you.

So we set our sites 20 years later on little babies who are bypassed. Notice the machine has only gotten longer and is now made commercially, thank God, by a little orphan company. Here is the gas dialyzer, and ECMO machine roller pump. Blood is drained out and pumped back into the little baby, and indeed it comes back always at a higher PO_2 and always at a lower PCO_2. It's very functional.

In Jay, who I convinced to do the first baby with us, and it was done about eight and a half years ago now, this is a baby who came in with PPHN. I'm not a baby doctor. You will hear much more about it later. With a blood pressure of about 50, and a PO_2 of about 50. We cut down the FIO_2 and made a little nitrogen space, so we could get the nitric oxide in it.

We gave the baby 20, 40 and 80. We only had a permit that allowed an hour of exposure, so we have to move along. The surgeons were all scrubbed and ready to catheterize the baby. The baby's PO_2 stayed up in the 200 range, and it didn't come down even after just an hour of therapy. It was an extraordinary first baby. It was a

knock your socks off first baby, and really what gave momentum and energy and the reason we're here today.

Jay did a number of babies, and it shows a similar thing. I won't show any more than this very early baby. It basically shows that some babies respond and some don't. This is a metabolic pathway to the chest we're learning about. It's the G pathway, alterations of guanaylate cyclase and phosphodiesterase. You can get other drugs to work in this, and we have just begun.

These fellows worked back to back with ours in the lab. They have done beautiful work looking for a full 24 hours. This is a funny number, for those of you who are not into it. This is arterial alveolar(?) oxygen tension ratios. Clearly, if you were perfect it would 1. You would be as good as LBLI(?). Indeed, you are far lower than that if you were a sick baby with PPHN.

They used lower doses 10, 20, 10, 5. Over the subsequent years since this has been, less is better. People are not using 40 and 80 nearly as much, except for the first few minutes of therapy, and then toning things down as they go.

So what has happened? Where are we? Let me run to the future, and say that ECMO is an expensive, complicated procedure. Much of the world will never do ECMO, never, ever. They could never afford it. It is

always effective at raising PaO_2. It requires invasive vascular cannulation, whether you are a VE or a VA folk, and I have been both, and it requires systemic anti-coagulation.

Although I know at present it is only about 60 percent effective in newborns, it is far easier to deliver and monitor. Notice we did those babies that I showed you around 1989 and 1990, and then published the groups of half dozen by 1992. I won't take credit for the reduction in babies in America being ECMO-ed. High frequency oscillatory ventilation and surfactant therapies are now used in infants, but certainly all three are having an effect. Where we were heading for 1,600 or 1,800, we're now barely holding at 1,000.

Let me say a word about ARDS, because some of your thoughts today have to be on that. The core problem in ARDS to me is not hypoxemia, it's pulmonary hypertension. In all injured lungs in adults, the mean pulmonary arterial pressure is doubled due to a marked increase in the pulmonary vascular resistance. There is tone in elevation of pressure, and I spent about 20 years trying to knock that pressure down.

Back 1985, back in history, we gave intravenous nitroprusside to try and dilate the pulmonary circulation and keep pulmonary hypertension from contributing to the pulmonary edema in the ARDS. The good news was that we

could get the pressure down. The bad news was we screwed up the shunt. We turned the patients blue and raised their shunt, and we knew it would never work intravenously with an NO donor to dilate the trunk.

So also came NO, and it worked so well in babies, it was hard not to dream that it might work microselectively. It's one thing to have a whole lung in spasm, and dilate a whole lung, but could it work in the little regions. If you think of pneumonia, good lung/bad lung, all kind of scattered and heterogeneous, could we dilate selectively in the ventilated regions of the lung, and steal venous blood into the ventilated regions, therefore raising the arterial PO_2, and decreasing the arterial PO_2 by dilating the shunting regions as you would with nitride, nitroglycerin, prostacycline(?).

To make a long story short, the first patient we did in Berlin, Conrad Wolke(?) could measure shunt independent of oxygen, which was important in this work. There you can see NO on, NO off, NO on. Pressure building down. This is a pretty bad ARDS. This is a girl whose chest has been crushed by a van. You can see the PO_2 coming up as we drop the pressure. We reverse, turn off the NO and down it goes.

This is not a drug that you have to dream a lot about. You can see it work in lots of patients, and that's

why it is appreciated so widely.

A word on dose response. This is Herbert Gerlock's(?) work from Europe as well. Looking at pressure, the ED50 might be something like 5 ppm, which is kind of the dose level that a lot of people are using today. But PO_2 is even more sensitive. You wouldn't think they would be equivalent in sense of the functions. Even here at 150 ppb -- that is what you breathed as you drove down Old Georgetown Road this morning in traffic -- even at 150 ppb, in ARDS patients, these are adults who can get an increase.

It also works for CO_2. We only talk about O_2 here, but there is that other respiratory gas, and it improves the removal of CO_2, so the VEDT(?) fraction always goes down in ARDS -- not always, but when we get these responses -- here is five for five. Anyway, Plebaise(?) and Company out of Paris, nicely shown.

It's got problems. Every drug requires us to pay something. What are our problems? The hemoglobin -- you have to measure, you have to watch it. NO_2 formation -- NO_2 certainly will do bad things to you. Withdrawal reactions. If you cold turkey the NO, you get pulmonary hypertension below the right ventricle.

Altered hemostasis. I'm sure you want to look at it carefully. We don't know enough. We think it's a mild effect on the platelets, but there is a CEMP effect in

platelet adhesion.

Mutagenicity -- we will all get cancer some day. It's kind of like smoking. Who knows?

Finally, if you got a very bad wedge pressure when you turn on the NON, you release the lung, you can go into heart failure. I remind you that when you in this room exhale, you are each exhaling nitric oxide. You are puffing about 4 ppb nitric oxide at the beginning at each of your exhalations. If you are bigger animal, you will blow a lot more, like an elephant, which is something like nearly 1 ppm in exhaled deep breath.

I'm going to end with this slide. I know it is not fashionable to worry about hypoxia anymore, but I remind you if you are in the trenches, and you take care of sick people, anoxia, as it is called, or hypoxia as it is known, is bad news. As doctors, we work real hard at rescue therapy. Don't forget.

Thank you very much.

[Applause.]

DR. PACKER: Let's proceed.

Agenda Item: Pathophysiology of ARDS - Dr. Dellinger

DR. DELLINGER: First, I would like to thank Dr. Packer, Dr. Lipicky, and the members of the Cardio-renal Advisory Committee for allowing me to make this

presentation. I'm Phil Dellinger. I'm at Rush Presbyterian-St. Luke's Medical Center in Chicago. I'm a practicing critical care physician, and have been involved with clinical research with inhaled nitric oxide in ARDS.

This morning I have been given a rather daunting task, which is in 15 minutes to go over the pathophysiology of ARDS and the potential role of inhaled nitric oxide.

This is a patient that I had an opportunity to take care, one of many with severe ARDS. This is one day into the course, the radiographical manifestation of ARDS, bilateral infiltrates, severe hypoxemia, significant shunt, absence of left ventricular failure. This patient was receiving very high oxygen concentrations, very high ventilator pressures.

If you look at the pathophysiology of ARDS, there is an insult to the endothelium, and to the epithelium. There is increase in thelium permeability. There is flooding of albili(?) to decrease ventilation and decrease transfer of oxygen into the capillary blood.

Causes of ARDS can be divided into primary insults, of which pneumonia and aspiration are the two most common, but also pulmonary contusion, toxic gas, severe drowning. Insults away from the lung that are associated with systemic inflammatory response syndrome, such as sepsis turns and multisystem trauma. Sepsis is the number one

cause of ARDS in multisystem trauma. It is also a frequent offender.

So now let's turn and discuss physiologic benefits in NO that are relevant to adult respiratory distress syndrome. These include improving oxygenation, improving right heart function, cytoprotection, and decreasing pulmonary capillary pressure.

Warren is already presented some slides depicting the benefit of inhaled nitric oxide in ARDS. This cartoon shows the disease state where here there is decreased ventilation relative to the profusion. Here is decreased profusion relative to ventilation. The rationale behind inhaling a selected vasodilator such as nitric oxide is that since the higher concentration of NO will be in the better ventilated areas, that you will get selected vasodilation, and attract blood to where the ventilation is.

I think if there is one thing we can all agree on about inhaled nitric oxide, it is clear that it raises the PaO_2 in patients with ARDS. Probably 60 percent of the patients will get a response.

This is the article that many of you first took note of the potential of inhaled nitric oxide in ARDS, an article by Willie Sible(?). It was published in The New England Journal of Medicine, showing the increase in PaO_2. Dr. Zimmerman will present some data on clinical trials on

ARDS.

Well, why is that important? Well, we treat patients with ARDS that go on the ventilator; have an x-ray that looks like this; and then suddenly ten days later have an x-ray that looks like this, a worsening filtrated disease, fair trauma, and now in a terminal state, because of progressive lung injury.

We don't know how much of that injury may be related to oxygen toxicity and ventilator support of the patient associated with iatrogenic(?) ventilator increase from high pressures, and something that is now called body trauma. There is ample data in animals to indicate that high pressures and tidal volumes are bad for the lungs, and there is no reason to think that that's not the case in ARDS. It's been more difficult clinically to link this to exactly what the effect is in ARDS.

Warren also showed the increased pulmonary vascular resistance in ARDS. This is associated with a strain and load on the right heart, and rationale would be that if you give inhaled nitric oxide, you will lower pulmonary vascular resistance and pulmonary artery pressure. If you do that, you will offload the right ventricle, decreasing right ventricle in diastolic volume, and decreasing right ventricle in systolic volume.

I think it is in clear in the literature that if

you give inhaled nitric oxide to ARDS patients, you consistently produce these effects.

Furthermore, if you look at right ventricular function, Rossaint and colleagues in Intensive Care Medicine in 1995 showed an increase in right ventricular ejection fraction in 28 and 32 percent.

Ficrobe and colleague in The American Journal of Respiratory Health Care Medicine in 1995 showed inhaled nitric oxide 5 ppm producing increased improvement in right ventricle function as measured by right ventricular ejection fraction of 32 to 36 percent in patients with ARDS.

I would like to now turn to a very controversial area, and that is inhaled nitric oxide as it obtains to cytoprotection in ARDS. I just had Dr. Sabo(?), as a visiting consultant in our division at Rush. This is clearly a very complex area. He has done a lot of work with pyroxinitride and now with PARS, and it is clear that you can set up experimentation using different methods, different concentrations of NO, different baseline states prior to NO administration; give it systemically, profuse it, inhale it, use different organs, and show a lot of different results as it pertains to cytotoxicity and cytoprotection.

I think when you look at the whole animal data within inhaled nitric oxide, where we are just looking at

the lung, the predominance of the data would favor a cytoprotective effective. Kavanaugh in 1994, in a whole animal model showed that inhaled nitric oxide decreases pulmonary vascular injury with edema. Poss in 1995 showed that inhaled nitric oxide prevents the increase of pulmonary vascular permeability caused by hydroperioxide.

Guidot in 1995 showed that inhaled nitric oxide decreases pulmonary capillary lesions. Ogura, in a large animal model, a swine model in 1994 with sepsis showed that inhaled nitric oxide decreased pulmonary edema. Guiterrez in an animal model in 1996, looking at oxygen injury actually showed inhaled nitric oxide improved survival in that animal study.

The only human study that I am aware of, that did not have a large number of patients, but looked at VAL markers of inflammation in patients with ARDS, Chollet-Martin published in 1996, showed that inhaled nitric oxide decreased VAL inflammatory markers.

So I present that information, because I think if you look at the whole animal model with inhaled nitric oxide with ARDS, I think the predominance of the literature would favor cytoprotection in animal model.

If you think about increased pulmonary vascular resistance in ARDS -- I'm going to put my two hands up. If you will let my right hand be the pulmonary venous thread,

and the capillaries are in between, and this is the pulmonary arterial bed here, if you increased pulmonary venous resistance or pulmonary arterial resistance, the right heart is over here, and that will put strain on the right heart from that increased resistance.

If you think about what the pulmonary venous resistance increase does, it actually raises pulmonary capillary pressure, which is an independent issue separate from right ventricular function. In ARDS it appears that the majority of the increase in pulmonary vascular trauma is in the pulmonary venous area, and therefore, the capability to increase pulmonary capillary pressure.

Benzing and colleagues spent a lot of their academic career studying this particular phenomenon, and have shown -- this is just one paper; there are several, this is 1995 -- that inhaled nitric oxide reduces pulmonary transvascular albumin clots in patients with acute lung injury, but furthermore showed that the mechanism was by decreasing pulmonary venous resistance, which can be measured by a decay in the pulmonary artery.

Again, if you decrease pulmonary capillary pressure, you decrease lung water, you improve PaO_2, and would be another route to decrease iatrogenic ventilator injuries.

Now in the remaining time, I wanted to move to a

very difficult problem, but a very important issue. That is, converting physiologic benefits from inhaled nitric oxide to clinical outcome benefits. The reason that is a challenge is that if you are asked the question why the patients with ARDS die, only a small percentage of mortality in ARDS is due directly to pulmonary response rate.

Suchtya and colleagues in 1992 showed a 16 percent incidence of pulmonary as the cause of death in ARDS. It's been reported as high as 28 percent by Montgomery in 1985. But if you have a drug that may produce a clinically significant effect in the pulmonary organ, but only a small percentage of patients with ARDS actually die from pulmonary-related causes, it creates a challenge in study design.

Both the study that Dr. Zimmerman will be presenting, as well as an NIH ARDS trial that is currently ongoing had endpoints of days alive and off mechanical ventilation. Which means that since this drug would only be expected to effect the pulmonary organ, that a more realistic test for the drug would be the ability to get people off the mechanical ventilator. Since patients with the shortest mechanical ventilator stay are ones that die early, you have to correct for the deaths by making the days alive and off mechanical ventilation. So that's what the study did.

Perhaps even a more realistic endpoint would be days alive and off assisted ventilation, since many people have to have to the endotracheal tube for reasons other than pulmonary dysfunction. Some have even argued that days alive and needing oxygenation criteria extubation would be an even more realistic endpoint, the rationale here being that inhaled nitric oxide, through all the things that I have mentioned earlier, would only be expected to improve gas transfer and oxygenation, and not be expected to affect things such as respiratory muscle strain, which may be the reason the patient continues to be on the support.

So in closing, and to address Dr. Lipicky's question where are we, and where are we going, which is why we are gathered here today, I think that where we are is that we still see deaths from ARDS frequently in our intensive care units. I think as a clinician, and if I was a patient and you did not oxygenate me by currently available methods, I would want this drug available to oxygenate me.

As far as routine use of inhaled nitric oxide, I think we need well designed clinical trials, and appropriate endpoints to decide whether this drug should be routinely used in ARDS.

Thank you, Dr. Packer.

[Applause.]

Agenda Item: Clinical Trials - Dr. Zimmerman

DR. ZIMMERMAN: Good morning. I'm June Zimmerman, and I'm from Baylor College of Medicine in Houston, where I am an internist and practice both emergency medicine and critical care in the county hospital. I really appreciate the opportunity to be here and to address of the data from the clinical trial on inhaled nitric oxide. I have to say up front that I have had a lot of input from the principal investigators from the French and European trials, who have been very gracious to share their information solely for the purpose of this meeting.

I would like to set the stage before talking about clinical trials to just point out some of the difficulties that we face in conducting trials in the syndrome of ARDS. The definition of ARDS that is used in clinical is it is a syndrome, so there are multiple etiologies of the lung injury. These various etiologies may impact not only the course and the outcome, but also the response to the intervention.

The way that you enroll patients in the severity spectrum may play a role in response as well. This is a syndrome that varies from mild manifestations to life threatening injury resulting in death.

The patient characteristics. We have to look whether these patients are medical patients. Are they

surgical patients? A young trauma patient is very different from the one I see that is 80 years old, has diabetes, renal insufficiency, and COPD. Obviously, these comorbid conditions, not only quality of the model disease, but the acute problems going on really impact the outcome, but in many instances the lung is not the determinant of outcome, it is actually the underlying condition.

In these patients who are very ill, there are many other interventions going on. Those varied interventions can influence the new intervention that detects this. Particularly in ARDS, you have to look at mechanical ventilator management as a possible confounding factor, but even such things as what type of nutritional supplementation is being used may be have an impact on the outcome.

Now if that isn't enough, there are some unique features when we are dealing with inhaled nitric oxide that have to be taken into account. First of all, the delivery and monitoring systems are not standardized. This may impact the actual dose being delivered. It also may impact the assessment of parameters such as hemoglobin levels and nitrogen dioxide levels.

Different studies have used various response criteria, and I'll point these out. In some studies response to nitric oxide is used as a criteria to continue treatment. The dose and dosing regimen varied tremendously.

This probably reflects the fact that we don't know the optimum dose for treating patients with ARDS, which may vary from patient to patient. How long patients get treated depends on the criteria for discontinuation. This also varies from study to study.

I'm going to start with the European multicenter study. Let me just caution you. There have been some conflicting data being kind of out there. This has not been published. I think we're on a little bit of shaky ground, so I'm going stick primarily to what the presentation by the principal investigator has been. This was presented last year in September at the French Anesthesia meeting.

This was a randomized, open label study. It was started in 1994, discontinued in 1996, because of slow enrollment. This is actually two studies. The enrollment was slow in the first study, so it was stopped midway. They revised their entry criteria and continued until it stopped in 1996.

They enrolled patients who had acute lung injury who had unilateral/bilateral infiltrates. They allowed both primary and secondary lung injuries. The majority of their patients had sepsis or pneumonia as the underlying etiology, and sepsis was about 15 percent at baseline enrollment. They required a PaO_2/FiO_2 ratio of less than 165 mm. Peak had to be at 5 cm water. They could have been ventilating

for anywhere from 18 to 96 hours.

Now this is the study that used response to NO as a criterion for continuation. They challenged these patients with 2, 10 and 40 ppm for 10 minutes, no longer than 30 minutes. If the patient had a positive response, an increase in the PaO_2 of at least 20 or 25 percent, and that number changed when they revised. It was originally 25 percent; in the second half it was 20 percent. If they achieved the positive response at any of the doses, that patient was eligible to be randomized for the study.

Now if they didn't have a positive response, they could rechallenge that patient every day for four days, and then they if they met the challenge, they could go on and be randomized.

Those patients who were randomized, were randomized to either receive inhaled nitric oxide or conventional therapy. Those that received nitric oxide had the initial dose, which was the dose in the challenge that resulted in the maximum increase in PaO_2. So it was 2, and they had similar increases with the higher doses, they started with 2. However, the physician, hearing from the patient, could change the dose to what was appropriate or optimum for the patient, so it varied considerably over time. That data has not been publicized at the present time exactly what was the exposure experience of these patients.

They allowed the patients in the conventional group, the placebo group if you will, to cross over to nitric oxide if they met criteria for severe respiratory failure. This protocol did not allow for any standardization of mechanical ventilation management.

The primary endpoint was reversal of acute lung injury. They used PaO_2/FiO_2 that varied between 214 to 205. This is interesting, because that was based on age. If you were over 60, you could use the lower end; under 60, the higher end. So it's kind of different from any of the other trials.

Secondary endpoints were the progression from severe respiratory failure, as well as mortality.

Now these are numbers that you may see that vary, depending on what information you have seen; 267 patients were accepted over 2 years; 180 responded; 87 were non-responders. So this is about 60 percent, which Dr. Dellinger mentioned in those who response with an increase in PaO_2, and this has been fairly consistent across most studies that looked at it. Ninety-three randomized received nitric oxide; 87 to conventional therapy.

The outcome data that is available showed basically no different in the clinical outcomes. The reversal of acute lung injury was 60 percent in both groups. The progression to severe respiratory failure, however, did

show a difference in that more in the conventional group progressed to severe respiratory failure. These were based on ECMO criteria, whereas only 10 percent of those receiving nitric oxide.

Mortality was 44 percent; 40 percent in the conventional group. This is statistically significant. I'll also point out that 18 percent of the conventionally treated group did receive nitric oxide.

Now what about adverse events? This has caused a lot of concern, mainly because there is a lot of misinformation out there. It was reported that there is a higher frequency of adverse events in the nitric oxide group. Let me just point out that when you have an open study, and you have only one group doing an intervention, it is quite obvious that it is likely that adverse events will be reported in that group, because you know you are doing something to them.

A higher frequency of sepsis and circulatory failure were reported. There is no statistical analysis associated with those. They do not appear to be distinctly different.

This is the one that caused some concern. Renal replacement therapy was reported to be more frequent in those receiving nitric oxide than the conventional treatment group. Again, there has been some clarification in some

communications from the company, but what it appears to be is renal replacement therapy includes not only treatment such as dialysis, but it also includes fluid management. In other words, they did hemofiltration for the fluid, not for renal support.

Also in many places in Europe, some of these continuous venous techniques are used to remove mediators, and absorb toxins, which we would not consider doing in the U.S.

Many of the patients in the NO group that had "renal replacement therapy" also had baseline renal insufficient on enrollment into the trial.

The problems with this trial were numerous. First of all being open. But many of the design issues, the changes midway through the study really makes it impossible for this study to make any conclusions about safety or efficacy given the problems. It does appear as an essential real effect is that nitric oxide decreased the development of severe respiratory failure.

What to make out of this? I think we have to wait for further clarification of exactly who these patients were, and what that renal replacement therapy was, which again, in many cases was not support for renal functions.

Let me go on to the French trial. Again, I will give credit to Dr. Didie Cayan(?) for providing some of the

additional details of this study. This was a double-blind study and randomized. It fit the standards that we would expect to see. The dose of nitric oxide was constant at 10 ppm. The placebo was nitrogen.

The interesting thing on this study is that they enrolled based on a Murray score, which is not a common factor in an ARDS trial. If they had a Murray score of 2-3, they were enrolled. There was no minimal feat required for entry. Both primary and secondary lung injuries patients were enrolled. In this study, two-thirds of the patients had sepsis on enrollment, so very different than the European trial, and obviously very different from the U.S. trial.

They also allowed treatment crossover, but this was a double-blinded study, so they could cross from either group into the opposite group in the study.

The also allowed termination at a PaO_2/Fi_2 ratio of 250. They checked this basically by putting the patient on an FiO_2 of 1 for four hours to determine whether they met these criteria. There was no ventilator strategy used in this trial.

Another interesting thing in this trial is that almitrine was allowed to be used. France is the only country I think that uses almitrine, which is a pulmonary artery vasoconstrictor. It is increase hypoxic

vasoconstriction. About 20 percent of the patients in both groups ended up receiving almitrine, either at baseline, or it was added during the treatment group.

The endpoints were the weaning of ventilation at a clinically relevant endpoint. Secondary endpoints were basically weaning of the gas, meaning their criteria for consideration, crossover rates, and mortality.

Their outcome data show no significant differences between the two groups. The number that came off ventilation was 34 percent for nitric oxide; 32 percent for placebo. Those that came off gas were slightly higher in the nitric oxide groups, 63 percent; 55 percent placebo.

This is somewhat interesting. The crossover rate is 12 percent in the NO group. A greater number of placebo patients crossed over to the opposite group, which makes sense if we were saying that they were not responding.

Mortality rates was 50 percent in the NO group; 43 percent of the placebo group. This is not statistically significant.

Adverse events -- this is information that has been provided to me by Dr. Cayan. They did not identify any safety issues in their trial. Specifically, they did go back after the almitrine information was disseminated, and looked at those who developed a creatinine greater than 3.5 during the study; 2 percent for NO group; 9.5 percent for

placebo. So no indication from this study that nitric oxide has a detrimental effect on renal function.

Conclusions from this trial. This was an appropriately designed trial. It did not show any evidence of clinical benefit in the patient population that they looked at. They also did not find any apparent safety issues from this trial.

This is one trial where we are a little bit on safer group in that the U.S. trial has been published in the Critical Care Medicine earlier this year, so we can kind of stand on those results at least. This was another double-blind placebo controlled trial, 28 days. This was a Phase II.

The American-European consensus definition of ARDS was used, which was basically bilateral infiltrates, PaO_2/FiO_2 of less than 300. We were aiming for patients who were early in their disease process, within three days of meeting criteria for ARDS, because we felt that those patients who had primary lung injury were more likely to benefit. Patients who had lung injury due to other etiology were excluded, and this included people with severe sepsis or had severe organ dysfunction. The outcome of these patients is more likely to depend on their underlying process, rather than the lung.

Patients in this study received nitric oxide

either at 0, 1.25, 5, 20, 40, or 80 ppm. After 60 patients were enrolled the 80 ppm arm was dropped.

This is the only clinical study thus far that has used ventilator management guidelines, and there were not mandates, but what we found was that investigators did buy into this, and did follow the guidelines fairly well in managing these patients.

There were 177 patients enrolled in this study. Just for your information, we looked at Murray scores. The mean in this group was 3.05. In the French study it was 2.67, for what that tells you. These are not comparable. Maybe these had a little bit more severe lung injury. The etiology of ARDS was primarily aspiration and primary lung injury.

Just a little bit of information about some acute physiology. Does nitric oxide increase the PaO_2? Yes. Using again, a very arbitrary response rate of 20 percent increase in PaO_2, we found that about 50 percent of patients met that criteria. We also found that is a very variable response in that not everybody responded; 39 ended up being responders at four hours. So it's a very dynamic situation. It's probably not a good criteria to use for continuation in treatment.

PaO_2 level for four hours, the mechanical ventilator planners were constant, and you can just visually

see the PaO_2 being increased. The ventilator changes to be made, as expected, the PaO_2 dropped to a level where we were aiming for, between a PaO_2 of about 80-100 in our patients.

Outcome criteria -- among the outcome criteria was days alive after reaching extubation criteria. These were criteria that were set that most physicians would attempt extubation. Now there are many reasons that people get extubated, or many reasons they continue on mechanical ventilation. So this is really a physiologic endpoint. What we found is that there is no significant difference between the dose groups. In fact, they appeared to have a little bit of advantage here.

The percent of patients who were alive and off ventilation at day 28, very clinically relevant, we found the percent in the 5 ppm. In post hoc analysis, this would statistically significant, but was not a primary study endpoint. So again, no big differences, but it does show perhaps that 5 ppm was a good dose to use.

Mortality could be viewed as both efficacy and safety, but this was not valid for efficacy. The overall mortality rate was 30 percent across the placebo and NO groups. Again, the 5 ppm shows a slight advantage, but not statistically significant.

Just to show you some of the safety issues that you maybe concerned about. Hemoglobin levels we found were

not elevated. There were only four patients who had levels greater than 3 percent; 2 of those in the 80 ppm group; in the 40 ppm; and interestingly one was in placebo.

You do see that at 80 ppm you have higher levels. If you were at 20 ppm or less, that usually is not a concern in at least the adult trials.

Now what about nitrogen dioxide? Here again you see fairly minimal changes with the lower doses of the 80 ppm. It is simply higher and different, but again not in the toxic levels. So in three patients where the it was greater than 3 ppm, these were all in the 80 ppm group that was left out early in the study.

Adverse events -- there were no significant differences in the types or frequency of adverse events. Looking specifically at renal failure, 9 percent in the placebo, and 11 percent in the NO group; not significantly different.

Looking at those who developed during the study a creatinine of greater than 2, 14 percent in placebo; 17 percent in the nitric oxide group.

So concluding from that that this was an appropriately run trial. It met our criteria and standards. It was discontinued. It was not powered to assess efficacy. It does not show evidence of clinical benefit that we could say is definitely there at this point in time, but neither

were there any important safety issues that were identified during this kind of a trial.

Well, putting all this together, what does it mean? I would defer to Confucius who said that, "Real knowledge is to know the extent of what is ignorance." I would say that we still have a lot to learn.

Specifically, I think we can say that nitric oxide improves oxygenation in ARDS in adults; not every patient, however. Clinical benefit is not yet proven, but we had many unanswered questions here. Are we choosing the right patients? Are we using the right dose? We need adequate powered studies to really answer that question.

At this point in time there does not appear to be a consistent pattern of adverse events, but continued monitoring for safety issues obviously needs to be part of our continued investigations.

Thank you very much.

[Applause.]

Agenda Item: Potential Toxicity - Dr. Abman

DR. ABMAN: I'm Steve Abman, and a professor of pediatrics at the University of Colorado School of Medicine. I'm board certified in pediatric pulmonology and pediatric critical care.

What I would like to do over the next 20 minutes is really briefly provide an overview, an outline of some of

the concerns that we have for potential nitric oxide toxicity, and what we currently know about it in this area.

Hypoxemic respiratory failure in the term neonate is associated with severe morbidity and mortality. Failure of conventional therapies to resolve hypoxemia often assess the case to me for life saving efforts such as ECMO, extracorporeal membrane oxygenation.

Although ECMO has recently shown in the collaborative in the UK to be life saving, it is associated with significant problems. It is costly. It is invasive, and it has significant morbidity and mortality in its own right. That is, it may cause an intracranial hemorrhage, pulmonary hemorrhage, as well as other acute problems, as well as perhaps late sequelae related to the requirements of cannulation of carotid artery.

This is a slide of a baby who died of a severe pulmonary hypertension, who died despite ECMO therapy. I should it not simply to illustrate the striking vascular remodeling that sometimes complicates this disease, but also to show you the striking pulmonary hemorrhage, all the blood you see around this airway. Indeed, this baby died of complications that related to ECMO, and partly to pulmonary hemorrhage.

The recurrent management of PPHN or hypoxemia in the newborn has certain limitations. That is, the standard

approach used mechanical hyperventilation or hyperoxia itself can cause significant oxidant lung injury or lung inflammation. For example, baro trauma or volu(?) trauma can lead to significant disruption of the epithelial barriers, worsening the lung disease. In addition, oxygen toxicity itself may play a role in the process.

In addition, babies who fail to respond to interventions often receive pharmacologic vasodilators such as tolazoline or sodium nitroprusside, however, these are limited by non-selective effects in terms of causing systemic hypertension, which may worsen right to left shunting, and cross the duct arteriosus or foramen ovale, and worsen the hypoxemia and gas exchange as discussed by Warren Zapol. In addition, often the response to such dilators are short, and not sustained.

Now one of the most common agents used currently is tolazoline. There are really aren't data from multicenter, randomized trials. This is an old study from 1979, which probably shows the largest clinical experience, but it illustrates that often the achieved response to this dilator is not sustained, and often there is a very significant complication rate. In other words, between the pharmacologic vasodilators, by use of mechanical ventilation hyperoxia, we can induce significant lung oxygen injury and inflammation.

Well, that's where the hope and excitement of inhaled nitric oxide comes in. As discussed by Warren Zapol, and as showed from our early experience in Colorado, we can improve oxygenation in babies with severe PPHN. As shown here, when treated at 20 ppm, followed by 6 ppm, we cause a rapid and sustained improvement in oxygenation in babies who met ECMO criteria.

The mechanism of course has been nicely discussed by Warren. That is, with the local delivery of nitric oxide in the terminal air space, it can diffuse into underlying smooth muscle cells, increasing cyclic GMP and cause vasodilation. Additional nitric oxide can then be metabolized by added binding by red blood cells by the hemoglobin, which is then metabolized in nitrites and nitrates. This then accounts for the selected vasodilator response as discussed by Warren.

I'll show this slide, and let's talk about toxicity. I want to mention that in the air space it's not just nitric oxide alone, but it's nitric oxide often in the presence of enriched oxygen, 100 percent oxygen. In addition, as you can see it's not just the smooth muscle cells or blood cells that are seeing the nitric oxide, but the diverse cell types throughout the line, including the epithelial cells or alveolar cells.

Other kinds of epithelial barriers can be

affected, and those are concerns that we must address when we think about this as a potential therapy.

Now nitric oxide itself, as you heard, is not a very potent or reactive radical, but rather what we are really concerned about is more related to some of the derivatives of nitric oxide, in particular, nitrogen dioxide or peroxinitrites. When we think about inhaled nitric oxide then in the setting of a large number of clinical experimental and in vitro studies, we have to balance the ideas of what are the effects of nitric oxide, that is the cytoprotective versus the potential cytotoxicity.

In other words, a number of studies have shown clearly a long list of potential cytoprotective effects, by lowering pulmonary vascular resistance, decreasing smooth muscle cell proliferation, decreasing muscle thrombosis, decreasing neutrophil adhesion, reducing incidence of injury, and perhaps decreasing permeability. All of these things are beneficial to the lung vasculature and to the lung itself in the setting of the clinical disorders we have been discussing.

However, on the other side of it we have significant concerns for this possible list of cytotoxicities. That is enzyme inactivation, especially in the mitochondria. Are we inducing cell death? Is there is a nitrosative stress, like so much of an oxidated stress?

Does it lead to surfactant inactivation? Does it increase edema itself? And finally, issues of mutagenicity.

So it's really this balance between cytoprotectiveness and cytotoxicity which makes it difficult to clearly discern what the net effects are in many settings.

What we want to do is briefly talk about some of these issues. We'll talk about the potential for lung injury in terms of exposure to nitric oxide, nitrogen dioxide, and perioxinitrite. I'll briefly refer to potential for mutagenicity, and then discuss issues like methemoglobinemia, prolonged bleeding time, and the problem of pulmonary hypertension of rapid inhaled nitric oxide withdrawal.

Well again, the toxicity of nitric oxide is less directly related to NO itself versus interaction with oxygen. We know that nitric oxide when metabolized forms methemoglobin, which can lead to tissue hypoxia by altering oxygen delivery. But these levels are readily measured, and as I will show you, remain low in most clinical settings with the doses used.

When it interacts with hyperoxia it can form other more toxic products such as nitrogen dioxide, which may cause epithelial damage, air reactivity, or pulmonary edema. Again, as I'll show you, the nitrogen dioxide level itself

can be measured, which hopefully will be protective of the lung.

The primary release is the generation of peroxinitrate, that is with nitric oxide with super oxide radicals, which can lead to peroxinitrite radicals, which then causes cytotoxicity, perhaps effective dysfunction, and leading to a scenario which looks very similar to ARDS.

Well, in terms of the hemoglobin itself, it is clear from the earliest studies that the with dose therapies this is rarely a problem, and can be easily and closely monitored. This illustrates our first 15 babies in Colorado on either conventional ventilation or high frequency, showing that although there is a rise in the hemoglobin levels, that these levels remain within our laboratory reported normal range.

In addition to that, you'll be hearing about later in a large, multicenter trial you'll see that at only the highest doses of nitric oxide does one see a significant methemoglobin development.

This is true also in terms of nitrogen dioxide formation. That is, that it is believed that at levels below 2 are fairly safe, but as one sees this data from a large, multicenter trial, the NO level remains at very low levels through prolonged treatment at various doses, except at 80 ppm, where we tend to see an elevation at this stage.

Again, the real toxicity that we're worried about is what we can't directly measure, and that's were a lot of us have concerns, and that's peroxinitrite formation, which can cause lipid peroxidation, causing cytotoxicity through that step; protein modifications; it can cause antioxidant depletion, and these kinds of steps are difficult to assess directly, because you can't measure peroxinitrite formation.

So if we think about nitric oxide in the protective roles, that is the decrease in inflammation, the vasodilation, and anti-proliferative properties, we have been worried, is it cytotoxic or is it cytoprotective. Then we turn to the whole animal studies that have been performed. Perhaps we can begin to tease apart some of the differences here in various animal models and experimental clinical settings.

The first study began to look at nitric oxide not in terms of when it is given as an exogenous agent through inhalation, but rather its endogenous role. It's important to remember that nitric oxide release in terms of endogenous activity seems to be enhanced in the variety of lung diseases and the setting of lung injuries. That is, babies who die of meconium aspiration, patients with ARDS have high trosilated(?) proteins, which were described by the first comments that were made this morning.

In other words, peroxinitrite is likely to mediate

some lung toxicity endogenous distinct from its effects as an exogenous treatment effect.

One study that was done by Peter Ward's group in 1991 was to look at a new complex related lung injury that caused an ARDS-type scenario. What he found was if you actually give a glocker of nitric oxide, you could actually decrease the permeability of these blood vessels in this lung injury model significantly compared to their controls. In others words, it looks like endogenous nitric oxide was contributing to the lung injury, raising many concerns.

On the other hand, in another model that was looked at, that looked at septic(?) shock in mice, they looked at survival in these mice following LPS treatment. You can see that there is a rapid and dramatic fall in survival between 24 and 48 hours. In this setting, however, if you block endogenous nitric oxide, rather than enhancing survival, you accelerate death. In others words, LPS administration, the blockade of endogenous nitric oxide marked worsening of survival.

These animals died with severe lung disease, characterized by severe lung inflammation that was far worse in these nitric oxide inhibited group than the group that received endotoxin directly. So if you think about endogenous nitric oxide, we have evidence in whole animal studies that it has dual roles. It's likely related to the

mechanism that causes the lung injury, but the majority of studies now are suggesting that there is a protective effective from endogenous nitric oxide in most scenarios.

To more closely explore this question, many investigators are looking at the effects of giving inhaled nitric oxide. This list is some of the animal studies that were performed. The studies listed on this slide illustrate some of the adverse events in this setting. That is, in the model of neonatal lung disease, inhaled NO at high doses over two days caused lung inflammation or surfactant dysfunction.

Now in these models the doses that were used were about 100 ppm, and as we have heard from previous speakers, the amount of nitric oxide being administered probably plays a significant role in the amount of monotoxic side products that are being generated.

One study has looked at in rats, the effects on lung development and lung growth, and reported decreased alveolar septation. This of course is a major concern in the developing lung, however, if you take a close look at this paper, what they really saw was thickening of the interstitial space, without a changing alveolarization, and the overall lung surface area remained unchanged.

Finally, there are a number of studies in which giving high doses of nitric oxide for prolonged periods had

no adverse events.

Well, along with the slides, I have suggested that we are seeing the adverse events or no adverse events, there have been a number of studies that have actually shown protective events. That is, in experimental models in whole animals that looked at the variety of different stimuli, this oxidant injury from oxidant toxicity or directly giving exogenous oxygen, ischemia reprofusion injury, premature newborn lambs with severe respiratory distress syndrome, cytokine induced lung injury, ischemic gun injury with associated lung disease, sepsis, allelic acid.

Many of these studies listed here have actually shown that nitric oxide has protective effects, that is they decrease oxidant injury, did prolong survival, and decrease lung inflammation.

This is one slide that was shown to you already, and it shows changes in permeability that is leaked to the vessels, and changes in pulmonary edema. It shows that in the presence of nitric oxide, you can dramatically decrease the rise in permeability of glutathione with oxidant stress here, and could decrease the development of pulmonary edema in this model.

Or Bruce Freeman's(?) laboratory, he looked at survival in rats exposed to hyperoxia, he demonstrated that expected mortality that is often seen in this model. Bruce

hypothesized, however, that the if he gave nitric oxide to these animals, he would actually accelerate the death through the generation of peroxinitrite, perhaps nitrogen dioxide.

To his surprise, he demonstrated a marked improvement in survival. These rats received hyperoxia with low doses of nitric oxide, and around a near 100 percent mortality is shown here, there is significant improvement in survival.

In another animal model, that is more relevant to the previous newborn, to the developing lung, is Dr. Sullivan in Colorado(?) gave nitric oxide to these animals to get decreased neutrophil accumulation within the lung. There are the control animals, all these red dots here, represent staining for neutrophils that are accumulating within the lung.

The NO treatment group demonstrates a lack of neutrophils, with a dramatic decrease in myeloperoxidase, suggesting protection from lung inflammation in this setting.

So the question is then in inhaled NO of pro-oxidine leads to these kinds of changes in vascular function, or actually serves as an antioxidant. That it's like driving super oxide through a different pathway or scavenging it, because it actually has that sort of

protective role.

Now a lot of controversy is based on the fact that in many models the effects are dependent on the dose used, the specific experimental setting. Especially in the in vitro setting, it depends on what kind antioxidants are provided. If they are glutathione, what's the pH? Many different things will shift the balance along these lines. So far the overall net effects of these of inhaled NO, at least in experimental animals, have been positive, suggesting protective effects in those areas.

Well, that's the animal studies. What do we know about the clinical studies? Dr. Dellinger told you already that in clinical ARDS there are very small numbers of patients. They measured interleuken-8 to the cytokine produced with lung injuries, which may provoke lung inflammation.

What they showed in the lavage fluid of these NO treated patients was that with treatment there is a progressive decrease in the amount of IO-8 that was recovered in the brachial fluid. In contrast, these are untreated control patients. They remained unchanged or perhaps increased a little bit, but this suggested some decrease clinically in lung inflammation.

The other piece of information that was, it was permeability of pulmonary edema. Again the Benzing work in

clinical ARDS suggested that independent of the hemodynamic effects, it may have a protective effect on the endothelium area. In other words, in these clinical patients, Benzing and colleagues infused labeled red cells and albumin and stand alones looking by this permeability index at the rate of albumin accumulation in the lung.

As you can see, it's a progressive rise over time, which during nitric oxide therapy, markedly decreased the rate of rise. Finally, following discontinuation of nitric oxide, there was again a progressive increase in edema. These findings suggest that independent of the hemodynamic effects, that there may be a direct terminability effect that my increase cytoprotectiveness instead of lung injury.

Well, the other side effects are more adverse events that nitric oxide may have. In other words, the bleeding time ratio itself is increased in patients treated with nitric oxide. You can see, however, that this has been controversial. A more recent study found that nitric oxide treated patients have decreased platelet degradation(?) in vitro, but did not prolong the bleeding time in clinical patients.

In other words, there were some significant reductions in the NO treated patients regarding platelet degradation assessed in vivo, however, the in clinical setting itself, as I did a bleeding time study, there were

no changes in bleeding time.

Now this of course is a very important question. We talked about the sick newborn in terms of the risk of intracranial hemorrhage. We will hear more about this later from the latest clinical trials, but so far in terms of incidence of intracranial hemorrhage and significant bleeds, there is no difference so far between the study groups.

The other response that can be an adverse event is this rapid so-called pulmonary hypertension following the withdrawal of nitric oxide or rebound. This is a child who is toxemic OI. You will hear about this from Dr. Kinsella. The child was toxemic. Her diaphragmatic hernia was treated with high frequency ventilation and nitric oxide.

After a period of treatment, was briefly withdrawn from nitric oxide, showing a dramatic worsening of oxidation. Resetting nitric oxide led to re-establishment of low OI again the second day. You find the third day the babies being off have problems with that rebound. This risk is itself is one that is managed clinically. If there is an awareness of this, it can be handled, and that is progressively over time it has been the trend.

Despite having this question of what nitric oxide may be doing in terms of vaso-reactivity in these patients, all of these patients tend to, over time, decrease this reactivity with resolution of their disease.

The other so-called adverse event is the in some patients pulmonary vasodilation may adversely affect their hemodynamics. This is particularly seen in cases with significant left ventricular dysfunction. For example in adults with heart failure, giving nitric oxide gives you an elevation of pulmonary capillary wedge pressure. Although pulmonary vascular resistance calculations tend to decrease, the elevation of which pressure perhaps falls in cardiac output can be concerned in this clinical scenario.

Well, in conclusion then, if one looks at the excitement about potential therapeutic roles, this is how we like to view the possibility of INO therapy: that is, it may have hemodynamic effects; effect on smooth muscle proliferation and growth tend to be favorable; anti-thrombotic in situ effects; perhaps by modulating inflammation, oxidant stress and permeability edema, diminish the risk of injury.

However, we need to learn more about this limb and this limb, and how to balance between these risks and benefits. Clearly, patients who are not going to be respondents to nitric oxide or improve clinically significantly shifts the balance between cytotoxicity and cytoprotection.

Patients at great risk for other kinds of toxicities in relation to fear of high morbidity and

mortality are likely to tolerate a given balance between the two. We need to continue to learn more about this balance. So far the net effect of the whole animal experiments, the clinical experience has been favorable, showing a net favoring cytoprotection.

Thank you for your attention.

[Applause.]

Agenda Item: Open Discussion

DR. PACKER: What I would like to do now is to open up all of the presentations that have been made this morning to discussion, and in doing so, emphasize that the goal today is not to reach any conclusions or develop any determinations as to whether inhaled nitric oxide is effective for any indication, but to really to achieve two goals.

One is to determine whether the data that exists already allows a conclusion in this matter, or whether additional trials are warranted. They may not be warranted because there is overwhelming evidence for lack of efficacy, or because there are sufficient concerns about toxicity that would prohibit the conduct of additional trials.

Furthermore, to determine if further evaluation of nitric oxide is warranted, that how such an evaluation can be reasonably conducted, because there are a number of issues in terms of patient population, trial design, dose,

and endpoint which have been raised by a number of the presenters today, and really need to be the focus of this morning's discussion, because it is the focus of this afternoon's questions.

So let me ask the committee to focus on that, and remember the goal here is different than the usual advisory committee. The usual advisory committee is to make judgments about efficacy and safety, and that is not the purpose today. The purpose today is to reach a sense of direction for the future, both in terms of whether this agent should or could reasonably be developed going forward, and second, how should the development proceed.

DR. THOMDONI: For Dr. Zimmerman, I think one of the issues that you emphasized is the develop of severe respiratory trachea(?) in the French trial was lower in the inhaled NO group compared with the control. One of the difficulties with emphasis on that is that some of the patients in the NO group, there was more mortality. So it's possible that the severe patients who got that actually died, so you are not seeing it. So I'm not sure whether one can really rely on that emphasis.

DR. ZIMMERMAN: Right, the patients that died earlier were not available for other interventions.

DR. THOMDONI: You had no chance to do anything else because they are already dead. So I think you have to

be very careful when you emphasize on thing to another, because look at the Tables on Page 6. You've got 12 percent in controls and inhaled NO too. On the next page the outbreak is 14 percent and the animal control is 6 percent.

DR. ZIMMERMAN: Right, and those are very small numbers. I don't think you can take a lot statistically from those. It's an observation. That was actually the European trial, which has lots of other problems.

DR. THOMDONI: Did you draw a conclusion from the European data and from your study is that although there are beneficial physiological effects in your study, the outcome advantages are not there?

DR. ZIMMERMAN: Right. The studies weren't powered to look at -- at least the U.S. trial is not powered to look at clinical outcome and efficacy. So I guess my point is that we still need that information. We need to obtain it in a very rigorous manner.

DR. THOMDONI: My last question, if you put all the studies presented, the European, French, and yours, there is really no clinical benefit as far as outcome is concerned. So do you think there is still in your own mind, a reason to prove there is something it, or should we discontinue it?

DR. ZIMMERMAN: I would say as a scientist/clinician I would not encourage anyone to try to

lump these three clinical studies together in any form. The European study has so many problems, I'm not sure to make of the data that are there. I certainly can't give you anything about efficacy.

The French trial is a well done trial. The patient population is very different. Whether that is the right one or the wrong one, but clearly you can't combine trials. You can't do meta analyses with these trials and try to come up with a conclusion. I would say you don't have evidence of benefit, but we have not tested that hypothesis well in the U.S.

DR. PACKER: Let me take the opportunity of having Dr. Zimmerman at the microphone and ask the committee and its consultants today to deal with an important question, how do you define efficacy in this disease? You described three clinical trials, each with different primary endpoints. If any further development of this agent in this disorder should go forward, one of the clinical factors would be what criteria does one use to judge whether the agent works?

You have already outlined, as I think others have, the complexities here. So cutting to the chase, what would you propose?

DR. ZIMMERMAN: Actually, I like the endpoint that we used in the U.S. trial. What I like as a physician is I

want my patients to survive. And if they survive, I would like for them to survive with a minimum amount of morbidity or none.

What is clinically relevant is if that patient survives, if I can get them off a ventilator two days earlier, that decreases risk for a lot of other complications. If I can get them out of the ICU earlier, that decreases their risk for other complications. So I think survival and off of ventilation, is from my perspective, a clinically relevant endpoint.

DR. PACKER: Let me just maybe ask further on this issue. I think many have emphasized that ARDS is a very, very complicated syndrome. That although there may be a pulmonary ventricular component to this disease, it is not the only pathophysiologic mechanism which is activated. The pulmonary toxicity and organ damage is not even a major cause of fatality.

There are all sorts of horrible things that can happen to patients with ARDS, not just dying. They can develop end organ problems of a variety of specific types. Why would you only focus on one endpoint? Why would you define the endpoint in such a way that it could only reflect the benefit of the drug, instead of looking at the effects in a more comprehensive manner?

DR. ZIMMERMAN: I agree with everything that you

have said. One of the difficulties -- what you're talking about is morbidity -- is defining morbidity objectively. That is the problem we run into with clinical trials. In other words, how much renal dysfunction is bad versus the good withdrawal threshold. That's really, I think, the problem. What you saying is absolutely correction.

A clearer indicator is getting them off the ventilator, less trauma risk, less lung risk, less GI bleeding risk. Or getting them out of the ICU, that also decreases risk we know. But matching morbidities is very difficult.

DR. PACKER: I remember our previous experience on this committee in this matter is complicated, because maybe a good analogy would the condition of acute myocardial infarction, where PVCs and the implications of PVCs in patients with acute myocardial infarction present only one possible thing that can go wrong in with acute MI.

So the analogy here is this represents only one thing that can go wrong in ARDS. Yet, you could define an endpoint in acute MI, death plus number of days off antiarrhythmic therapy, but none of us would be very impressed by that.

DR. ZIMMERMAN: Well, I think it's a little bit different in the setting of ARDS in that we clearly know the risk of mechanical ventilation in the patient.

DR. PACKER: We know the risk of antiarrhythmic therapy too.

DR. ZIMMERMAN: You're right. I guess I'm not as comfortable with MI as you are, obviously. By decreasing the risk, again, we know there is pulmonary lung and GI bleeding, multi-organ failure progresses along with this. So I don't know what other endpoints fit that is going to tell what impacts the outcome of the patient. We don't have enough information, plus it depends on the population that you choose going into the study, as to what you what choose.

DR. CALIFF: This is more a comment I guess, and I'd like to have your opinion on this. At least what the committee, I would argue that time on the ventilator or time in an intensive care unit is not a surrogate endpoint for predicting future values. It may be that too, but it actually is a bad thing. If you ask a patient, would you rather be on a ventilator or not on a ventilator, would you rather be in an ICU or not in an ICU, I think the patients would unanimously, unless they were crazy, say that they would rather not be on the ventilator.

In a variety of settings, having less ventilator time in clinically significant amounts, or less ICU time, as long as other bad things didn't happen, and there was no increase in mortality, I would argue that the clinically relevant, measurable benefit, just like hospitalization for

heart failure or hospitalization for patients with heart disease, you would rather avoid that.

I'm trying to say between a surrogate which is totally meaningless to the patient, because it is a signal that would happen, and the non-fatal clinical endpoint, which is very important to patients, and may or may not offer surrogates.

DR. ZIMMERMAN: Yes, and so we could pick another endpoint. You could say the number that have renal dialysis or renal replacement therapy. The problem with choosing something else is that the incidence is lower. You don't know enough about that particular endpoint to feel comfortable designing a study to measure a difference in that in a blinded study. Mechanical ventilation is easy to measure objectively -- well, it's not totally objective, but it may have some relevance.

DR. PACKER: Rob, let me take what you just said and see if I can I understand what the implications of it would be. I don't think one would say that being on a mechanical ventilator is good idea, but mechanical ventilation is largely the saving of ARDS, used to manage the problem which is physiologic, which is a certain level of PO_2.

So that the mechanical ventilator here is actually used to treat the physiologic measure of PO_2. It's

discontinuation is determined by what the level of PO_2 is. It's institution is determined by the level of PO_2. So if you had an agent which makes the PO_2 go down, one might anticipate that the use of mechanical ventilation would work -- its use would be in parallel with the levels of PO_2. That's only one issue.

The issue I'm actually really concerned about is the fact that it could be that the use of mechanical ventilation is only one of many, many morbid events in these patients. In fact, depending on the patient population and the type of ARDS, it could actually represent a very small amount of the morbidity of this disease.

It is possible that an agent being developed for ARDS could have an effect on mechanical ventilation, and that would be desirable, but it would have either no other effect on any other heart syndrome, or even a slight adverse effect, not statistically significant, and not easy to interpret on other more morbid events in ARDS, so much so that the net clinical benefit is not apparent. That's my concern.

DR. ZIMMERMAN: Well, that's why in the U.S. trial we tried to avoid sepsis and multiple organ failure for that reason. And that we knew from sepsis trials that the lung played no big, permanent role in determining outcome. Sepsis and multiple organ failure did. I think that's what

you are getting at.

That's the population where NO may not make a difference, and that's why we elected not to do that population. That's not to say that it still may not benefit those patients, it's just going to be a lot harder. The numbers have to be a lot larger to detect a difference in those patients.

DR. CALIFF: Just one more comment. It does seem the more we learn, the harder this gets. I would just argue that mechanical ventilation in most people with ARDS actually does represent a pretty overall synthesis of what's happening with the patient. There is no take him just based on the PO_2. They really have to be in good enough shape to care for their airway, and have adequate respiratory function in a lot of other ways.

So it's a pretty good overall measure of how someone would with a survival issue with lung disease is doing. But it is in murky in a way, because of the issue that you brought. You may improve mechanical ventilation and make something worse.

So I think we would all agree that in the ideal world we might could have a trial that might have this kind of composite. It's like heart failure trials at pre-admission, which would be large enough to detect moderate sized adverse effects.

DR. PACKER: But like in heart failure trials, where we can get ourselves into trouble when we define morbidity in a cause-specific manner, and combine them selectively. That's my point there. What we have learned now in many other cardiovascular traditions is that we are on much safer ground when we look at morbidity in a more comprehensive, all encompassing way.

My major point here was this was a very focal definition of one type of morbidity, which is now being raised to the level of primary, and is not comprehensive. That's the distinction.

DR. CROSS: In adult critical care, this is one of the noisiest conditions you will find in terms of many of the factors that are determining the patient's outcome. About 15 percent of deaths are related to respiratory failure. I think that's right on target. There are a lot of other conditions, a lot more renal failure and sepsis that typically produces death.

It is hard to measure benefit. Mortality is one. At least in Seattle over a decade, without a magic bullet, without any sort of curative treatment, really just better care all around. I think this is something that kind of falls in that area. This is a thing that I would expect to improve mortality without having an appropriately powered study.

As a result, I think appropriate endpoints need to be directed at measurable goals that have true meaning, and to measure the risk that the patient derives from that. It is a real benefit to be off the ventilator a couple of days early, and not just from the discomfort of it, but also the risk for ventilator-associated pneumonia and secondary problems. So I wanted to certainly support that idea.

I think morbidity -- making sure that we're not making an improvement in one area, but at the cost of another area is an important point. I think the trends that are favorable trends of mortality that we are good markers that probably we're on the right track with that; that we're not causing other serious morbidity that is likely to lead to a problem with increased mortality. It would be nice to measure morbidity in a more comprehensive fashion.

DR. LIPICKY: I don't think the way to look at this is as a surrogate, because it implied that mortality is going to get better. I think the disease has been reversed or altered in its natural history. It is indeed a clinical benefit not to have to walk with a gas tank, so it is a clinical benefit. It isn't as a surrogate for something else.

Indeed, as you know in other diseases we are perfectly willing to make judgments on the basis on how long people can run on the treadmill, and it's a form of

intervention.

DR. PACKER: I think the issue is not at all whether it's a surrogate. The issue is whether it is comprehensive and an accurate reflection of the clinical progress or lack thereof that a patient with ARDS has achieved at a certain point in time.

DR. LIPICKY: But if you would be willing to accept it as a non-surrogate, you would only want it to reflect the change in the natural history of the disease or a surrogate for that. It is not a surrogate of how the disease is going.

You can't view in with no indication at all as to whether or not the disease has been altered in its natural history. It is an independent clinical benefit. The disease might in fact get worse, or be totally unaffected by having benefit in that area. So it isn't a surrogate. It's not playing the role of reflecting change in the natural history, but you have to accept that. You may not want to.

DR. ROTHSTEIN: A couple of remarks. About 30 years ago we removed oxygenation as a cause of death in ARDS. Since then we have been struggling to eliminate causes of death, and we have not done a good job of it. It's been slow. It's not necessarily been a great use.

I'm sort of getting a chuckle out of this, because you picked the most complicated disease state, as an issue

to look at and discuss. The reason I'm getting a chuckle out of this is because for the last 30 years I have lived in the land of off label uses. I think there are going to be much clearer indications and endpoints for this agent. It may in fact be that ARDS, adult ARDS becomes the off label use.

I don't think we're smart enough yet to know what the endpoints are. It may in fact be a decreased in the ICU, reflected in the decreased infection rate in these patients. I don't know, but we have to come up with those endpoints. Those may come out over the course of time.

DR. PATTERSON: Can I make a comment? My name is Alan Patterson from Washington University.

I think that perhaps the lack of benefit or improvement in mortality as seen in the adult ARDS patients may reflect more the timing of its implementation as therapy, rather than whether it actually does any good.

There are models of early lung injury exclusive of any other organ injury. The best model of that is lung transplantation. We've got the biggest pediatric lung transplant program in the world. We have a large experience with the use of inhaled nitric oxide. Lung allograft reprofusion injury is the commonest cause of morbidity and mortality following lung transplant. That is dramatically reduced by inhaled nitric oxide when it is used in the

beginning, right as soon as the injury is evident.

It reduces time on ventilators. It reduces ICU stay. It improves oxygenation, and improves mortality, and reduces the need for ECMO.

It is also interesting that if you administer inhaled nitric oxide in donor lungs, it improves their function following implantation. It is kind of an interesting side light measure, but it is well explained by its various mechanisms.

So I think lung allographic reprofusion injury represents a very early form of ARDS, and untreated goes on to look like any other ARDS. Perhaps if had some implant in this therapy early on in the course of ARDS, it might have a significant impact on ultimate outcome.

PARTICIPANT: Just a couple of quick comments. I think even removal from mechanical ventilator as an endpoint handicaps the nitric oxide somewhat, because many patients remain on the ventilation in the tracheal tubes, which this will not have any effect on early protection or for respiratory muscles. I think there is no reason to think this drug will affect respiratory muscle strength.

So to some degree, if you think about the physiological effects of inhaled nitric oxide, even removal from mechanical ventilation becomes a fairly tough endpoint. I think it's reasonable, if you do get some endpoint, that

you would need to look carefully at all the data that has been gathering, to feel comfortable that there are no safety issues, but I think that can be done.

As far as should we still be testing inhaled nitric oxide, I think there are enough problems with the other trials that unless somebody sorts it out for me, it really doesn't help me at all in making any kind of decision. I think the French study is a worthwhile study, hampered somewhat by having a high number of sepsis included. I think most of us feel that group is not going to have as likely enough as patients that have no septic area. So that was certainly handicapped.

In our study, we need to see what the 5 ppm does with that post hoc analysis.

DR. THOMDONI: I think one of the difficulties in this area, depending the critical care area at the present time in cardiology where we do the best we can. Then we show all right, we have done the best we can, and the we send the patient to the general ward. We are glad that this patient is out, because we have patients who die in the hospital.

So I think you have to take a composite endpoint. It's nice that you are going to use the hospital stay for when a patient comes off the ventilator, but suppose you do an comparison. That is, you oxygenation. You are out of

the intensive care unit, and yet there is a very prolonged hospitalization and dies.

So I think it is very difficult for me to accept one surrogate endpoint. You have to take a composite endpoint of death, hospital stay in ICU, and what happens to the patient when they leave the hospital; has the lung been damaged or not? So one could come up with an algorithm of this for sample design.

Suppose more patients on NO inhalation, and yet in the remaining patients you are reducing the time to ventilation. Is it good or bad? A disease with different morbidities in different patients might be the answer before we started using the agent, even as an approved indication.

DR. PACKER: I don't think that the data about the number of days off mechanical ventilation -- in fact, I don't think anyone has heard that it could not include mortality. I think everyone actually feels comfortable it's not a surrogate. I think the issue is whether it is as a measure, sufficiently representative of patient outcomes.

DR. THOMDONI: I think that should be made a surrogate endpoint. What you really need is a mortality, improved stay.

DR. ZIMMERMAN: Total hospital stay is very a subjective endpoint in that the criteria for discharge varies with when the insurance runs out, as well as family

issues. I'm not sure that's the appropriate one.

The other thing you get into when you start looking at hospital stays when they die are ethical issues. In other words, quality of life. Would somebody want to be alive for an extra week, and yet still die? I think that's a little bit harder. I think mortality really is part of this efficacy or part of this analysis. I agree that's not a substitute for that, but hospital stay is a little bit like ICU stay. Those are more subjective. They are reasonable to report. I'm not sure what you do with that information, how to apply that to evaluating a drug.

DR. THOMDONI: What do you with a patient -- I'm sure you have seen a patient who came off the ventilator, and you said, we'll you've done your best, and you're going to send him to the hospital ward. It may not die with [unintelligible] failures. I think you have to take it from Bob's endpoint, just not in isolation.

I realize it's very important. I don't want my patient to come back if I can avoid it, but there are times you could also argue perhaps more time on the ventilator, the patient is so tired that his muscles are now working might be beneficial. We are presuming that the short run is actually going to improve the total outcome. I don't think I have seen any data presented about that. It could be true, it could go the other way. Maybe one or two days more

of ventilation, the guy can't breathe he's so tired, it might be beneficial.

DR. ZIMMERMAN: No, I don't think mechanical ventilation is going to affect their ultimate outcome. We just do know it decreases risk. But when they are alive, no, there is nothing to suggest that.

DR. LIPICKY: But I think you have to bear in mind that there are two clinical goals that are appropriate. One is feeling good, and the other is living longer. It's okay to have to have people live shorter if they feel good while they are living. Those are trade offs that patients and doctors can make decisions about.

If you are willing to accept the oxygenation, the time off ventilation -- and I'm making a rough analogy now -- as a feeling good thing, it is not also necessary to have that same treatment to make you live longer in order to be an accepted treatment. In fact, it could make you live shorter, and still be an acceptable treatment if you know what the magnitude of the effects are, and it's adequately described.

So I don't think it's necessary to think in terms of having combined endpoints, but it certainly is necessary to have those things measured.

DR. PACKER: I think the problem Ray, is that as opposed to many of the diseases we normally see come to the

committee, at the trials which are enrolling patients with those diseases, and as you know these trials are pristine in their ability to enroll patients with nothing else, just the disease being studied.

Therefore, one can reasonably say if someone has less pain(?) in a clinical trial, that they actually felt better. In this disease, the determinance of feeling good is not one. There is not one determinant of feeling good. There are multiple components of feeling good. That is what I think makes this more challenging.

I'm not right away advocating the superiority of a more comprehensive measure of morbidity. I am just wondering what trouble we can get into if we don't have one, and that could we potentially approve a drug that actually has a very, very tiny therapeutic benefit because the endpoint is defined in a very, very cause-specific manner.

DR. LIPICKY: Would you feel more comfortable if the endpoint were alive, off ventilator, and a response to the questionnaire that said I feel good?

DR. PACKER: One question in that questionnaire?

DR. LIPICKY: Would that be better?

DR. PACKER: No, because I think that first of all it would not be very discriminating. Most patients who have been excavated feel better than they did when they entered the hospital.

DR. LIPICKY: But isn't that feeling good?

DR. PACKER: I'm not certain there is an added value. I understand the purpose of the question.

DR. KONSTAM: I'm a little bit more comfortable maybe with the possibility of using time on a respirator or time off the respirator alive as an adequate endpoint. I mean I think your point is very well taken that this is a complex set of disorders that the patients are experiencing, although then again the commonality in this condition is respiratory failure. That's why it is called ARDS.

It would be great if you could come up with some kind of score that represents the composite of how the patient feels and how they do, but that's different from him. So if you are looking for an endpoint that examines some index of the respirator status or success at improving the respiratory condition, it then, as Ray is pointing out, is meaning to how the patient is doing, because they don't have to be tied down to the respirator.

Throw in the point that Rob made, that you are going to look for other evidence that something else is going on in the other direction, so you if have greater time off the respirator, but you more patients on dialysis as one of the studies suggested, that would be a problem. But you don't see any of those things, and you are left with this one semi-concrete endpoint of being off the respirator, I'm

fairly comfortable that I would like to look at that.

DR. PACKER: Although I totally agree with you, the only problem I have is the fact that it is almost impossible enter the data on safety into your primary endpoint in any kind of reasonable or prespecified manner.

For example, if you had a statistically significant reduction in the pulmonary benefits, the drug was better at keeping people off a ventilator or getting them off the ventilator early, and you had a nonsignificant increase in the number of the morbidities, but it is not significant. See it's elusive. The concerns are elusive. The total benefit in treatment versus not can in fact be far smaller or non-existent if you factor that into the pulmonary equation.

DR. KONSTAM: I hear you, and these are very valid points, but I fear that you could wind up handcuffing yourself. If you decide that pulmonary insufficiency is a major component of the syndrome, it is in fact a common denominator. If you are seeking therapy that influences that particular part of the syndrome, I think you are going to look for an endpoint that is a marker of that piece.

Granted that what you are pointing out really is the imperfects of the trial endpoints, other than mortality. If we could a mortality study, I think that would be fantastic. Short of that, I think we're going to wind up

handcuffing ourselves not to take the respirator indicator.

DR. TEMPLE: In some ways this is not so different from the problems that this committee has faced before. When you approve a treatment of suppression of super ventricular arrhythmias with flecainide or something like that. There's always a concern that somewhere underneath this you are harming someone. So one of the things is how much assurance you have that you haven't made other things worse. This is in some ways, not unsimilar.

I would be interested in hearing off the top of the head feelings about who much assurance one might want in this case. I mean if you are going to accept a useful, but not ultimate benefit like being off the respirator, I guess my assumption is you would not trade a great deal of excess mortality for that benefit. Probably you would want to make sure there wasn't any.

What sorts of thoughts do people have in mind about how much -- I mean if they had a bad lean on mortality, which is an outcome that could be tolerated.

DR. ZIMMERMAN: I don't think anyone has said they would trade off an excess mortality just for coming off the ventilator two days.

DR. TEMPLE: Right, I understand. How much assurance that there isn't such an excess would one need? Do you have numbers in mind?

DR. CALIFF: One way to frame that question is to ask the question how much of an increase in mortality would you want to be able to be able to exclude? In other words, if you look at the data we currently have, the confidence interval would include up to something like a 15 or 20 percent higher mortality.

DR. ZIMMERMAN: I don't think I would have a ready, specific answer. Is it 5 percent excess? Is it 2 percent? I think if you polled all the critical care physicians just in this room, we would come up with a wide variety. Certainly, I would say 5 percent or less, but I'm not sure that even comes close.

DR. THOMDONI: I think it is such an important issue because in intensive care you want to get the patients out obviously alive. That's your whole purpose to admit them. If there is any more mortality, how you can associate the two, I think is impossible. You are admitting them so that they could probably live a useful life and survive.

Say if your respirator weaning off red is 10 percent better in your NO group, and your mortality goes up 8 percent, it would be very discomforting.

DR. ZIMMERMAN: Oh, I agree.

DR. THOMDONI: You have to take a combined endpoint and make sure that they are not going out of the direction --

DR. ZIMMERMAN: That's why mortality is factored in.

DR. THOMDONI: You have to put it in.

DR. LIPICKY: You should answer Dr. Temple's question he just asked you. Pick a number between 1 and 1 billion, and say what you think off the top, what you think the percent is that you would accept. All I want is a number.

DR. THOMDONI: To calculate that you are confident that you are not causing excessive mortality.

DR. LIPICKY: What number would you be comfortable with? That is the question -- 1, 2, 5, 100, 10,000?

DR. THOMDONI: It's not a question of 1 or 2 percent. I think you have to say see 300 patients, and if I lose 5 versus 2, and if I benefit 3 by coming off the ventilator, I would be very nervous. I want to be sure I have not done something else.

DR. LIPICKY: No, but that's incorrect.

DR. THOMDONI: I realize that.

DR. LIPICKY: It's what confidence you want to have in excluding how big a percent. Name that percent. Then you can size the trial and figure out what you need to do.

DR. PACKER: I suspect that they will already have their hands full trying to size the trial for the primary,

let alone trying to size the trial to provide persuasive evidence for safety that guarantees that any committee looking at the data retrospectively not raise some concern about some numerical difference between two columns.

In fact, I'm actually less concerned about factoring in mortality, because mortality is already being sort of factored into this primary endpoint. I'm more concerned about what do you do when you have a result in a trial -- for example this is the European ARDS study, where this is just one column, renal failure, 29 percent in control, 44 percent in inhaled nitric oxide. Nominal P value 0.05.

It's not factored into the primary endpoint. How much weight do you give that? How many renal failures do you worry about to offset 1.3 days shorter on the ventilator?

DR. ZIMMERMAN: I think what you have raised is how factor in safety versus efficacy or with efficacy? I think until you actually see the safety data, it's very difficult. I will just object to using European trial data.

DR. SESSLER: ARDS is incrementally tight. It's a multiple organ failure in all regards, that that's really a key area that we need to look at. First of all, a lot of people who look at ARDS in general consider it the respirator component of multiple organ failure.

Secondly, if the degree of organ failure during the time of mechanical ventilation will also impact also on the ability to remove the patient from the ventilator. So it's not just an oxygenation issue there either. If the people develops sepsis and renal insufficiency, and has more problems with fluid and so on, they may require a longer ventilation time, even though the drug has been effective.

The thing is that worsening morbidities really can be measured to a certain extent by looking at multiple organ failure. There are a number of scoring systems out there that might be used to look at incremental changes after randomization to see if the change in multiple organ failure score is different between the two arms.

If there is no change, and there is an improvement in the time off of ventilation, and there is no difference or a trend towards improvement in mortality, I think you have clearly demonstrated that the drug is effective, and you have demonstrated that there is not excessive morbidity associated with it. So that may be an option worth considering in a way of trying to measure in more of a comprehensive fashion perhaps, morbidities that might result inadvertently from using the drug.

PARTICIPANT: I just wanted to clarify something in response to something that you said, Malcolm. That is that there is a big difference between the natural course of

the disease endpoints and the feel good endpoints. The committee has said, and we have sort of agreed that in considering hard outcome endpoints it is much more comfortable to look at net effects. That is dead is dead, and looking at cause-specific death may be imprudent if the drug is associated with additional other causes of death, which balance or even out-balance the deaths averted from the original disease.

Now in connection with feel good endpoints, we have not in general, looked to net benefit. It's possible to look at net benefit. Occasionally people looked at global questionnaires -- how do you feel compared to the way you used to feel, and stuff like that. But it is also true for example that in angina we say with nitrites it is sufficient to demonstrate that an anti-anginal product lets people run longer on the treadmill.

Well, many people will say, yes, I can run longer on the treadmill, but this headache is so bad, I would rather have my chest pain. Now the thing which is different is we know we are not approving a placebo, and the patient can, on the spot, make that choice. I don't want to take this anymore, I'd rather have my chest pain, et cetera. Or I don't want to take clonidine for it's antiarrhythmic symptomatic benefits because the GI toxicity is just unacceptable to me. That's fine.

If one is talking about irreversible endpoints, and I'm not sure where the renal thing comes in here. Is this a permanent renal deficit, and the person has changed the natural history of his life? Or is this just well, you have a few episodes or something like that, and it fades off in time? The idea of looking at net symptomatic benefit is not necessary at all.

DR. PACKER: I'm glad you mentioned the last component of that, because if it is permanent, if it is not reversible, the equations are very different. If it is something which is identifiable and reversible, then the judgment can be made on the spot. If it is irreversible, it has to be factored in, and it's hard to know how to do that. I think that's what we are saying.

DR. KORNFIELD: I'm a pulmonary critical care physician.

DR. PACKER: Name please?

DR. KORNFIELD: David Kornfield. I take care of primarily pediatric patients. Perhaps one of the difficulties in trying to answer this question with respect to ARDS is the diverse nature of the disease states that we treat. It is probably clear that one of the most severely affected patient populations is those patients with bone marrow transplant and acute respiratory failure.

Generally, I think people have believed that there

is about virtually a 95-100 percent mortality risk in patients who go on to mechanical ventilation with bone marrow transplant. We have a pretty long, or reasonably good sized experience with patients who have respiratory failure in BMT, in the bone marrow transplant world.

In our non-blinded trial before we went to a blinded trial, which we are now part of a multi-center trial, we definitely had a decrease in terms of mortality in patients who had bone marrow transplants and were on the ventilator. The data is now just emerging from our multi-center trial. I don't have the results, but the early analysis does to seem to suggest that there is some change in terms of mortality in this patient population.

I guess if people were really interested in whether or not inhaled nitric oxide had an effect on mortality, this might be a patient population where you could really look and see some changes. While it is probably premature to say, the clinical sense is that some of these people do survive.

We have had patients, without meaning to talk too anectodally, who have had aspergillosis, who have left the bone marrow transplant unit, and that was virtually unheard of prior to the inception of nitric oxide as a therapy.

DR. PACKER: Yes, please identify yourself.

DR. BENNETT(?): Rich Bennett from San Diego. I'm

a pulmonary critical care physician talking care of mainly adults. I actually have also had an opportunity to have extensive experience in pulmonary vascular disease, chronic pulmonary hypertension, which maybe we'll be able to discuss later.

With the ARDS population I guess my thinking about it is maybe we're asking too much of this agent. What we know about NO, and I think the data shows it, is it has a clear physiologic effect similar to a hypertensive drug that lowers blood pressure. Trials demonstrating reduction in blood pressure of any hypertensive, if coupled with lack of toxicity and morbidity are usually grounds for approval.

The drug approves PO_2 in more half the patients, dramatically in many cases. If we can demonstrate lack of mortality, as you are discussing, coupled with that physiologic endpoint, shouldn't NO then be a useful adjunctive treatment for ARDS? Are we asking too much of it to define these complex endpoints?

DR. PACKER: Let me try to address that. There is a reason why drugs are approved to lower blood pressure, which as you correctly describe, is a physiologic parameter. That is because there is overwhelming, compelling, persuasive evidence that there is a relationship between blood pressure lowering and a reduction in morbidity and mortality in patients with hypertension.

I guess we have not seen any evidence, let alone persuasive, compelling evidence that a relationship exists between changes in PO_2 and outcome in patients with any disorder, particular ARDS. Do you have such data?

DR. BENNETT: Not specifically. We certainly know that data suggesting that oxygen toxicity is a bad thing, and the ability of an agent to lower oxygen needs, which we know NO does, we have that data, is I think, reasonably well demonstrated to reduce the risk of oxygen toxicity. So I think we could support that.

DR. PACKER: Does any member of the committee or its consultants -- would any of you advocate using changes in PO_2 as a surrogate endpoint to support the approval of this drug or any other drug of this type for any clinical indication?

DR. ZIMMERMAN: I will answer that and say no, because that's again, just raising a PaO_2 has no clinical relevance to the patient or the physician caring for that patient. It has to be coupled with some other benefit, such as survival, decrease in morbidity, something else. I think you're right, we don't know that raising a PaO_2 is the surrogate. In fact, we probably know that it's not. So just physiology I don't think is what we are aiming for with this drug.

PARTICIPANT: Well, I think it has a major impact

in the management of a lung transplant patient. It determines precisely the time of excavation, mobilization from the ICU, discharge from the hospital. So we rely upon that measure very importantly in the management of patients who have a very early and transient lung injury associated with the reimplantation response or pulmonary reprofusion injury.

If you want a clinical scenario --

DR. PACKER: The concept here is not to engender an open debate on the issue. The concept here is to ask whether there are data that would allow us to make irrefutable connection between changes in PO_2 and outcome. I guess I haven't heard anyone here say that there is.

DR. GRINES: I have a little bit of difficulty, because this is out of our area of expertise. Many of the things that have been approved in the past, it's my recollection at least, that we did not require evidence of sepsis, renal failure, mortality. One of the disease states actually is heart failure. We approve heart failure drugs because they feel better. It reduces their incidence of heart failure. It reduces their incidence of readmission. I would think that ventilator time might be a similar type of outcome that we can follow perhaps.

The second thing is maybe if there is anybody in the audience who has this information, I'm curious about

these other methods of managing patients with ARDS and hypoxemia, and how they were approved specifically -- ECMO and some of the other adjunctive treatments.

DR. ZIMMERMAN: There are no other interventions. That's the problem. Just mechanical ventilation techniques that people are looking at, prone positioning, other clinical trials with other drugs, almitrine being what France has used. Right now we don't have anything else other than our mechanical ventilators. Ketaconasol(?) has been looked at; steroids, obviously not early in ARDS. That's one of the dilemmas is we don't have anything else that has come through like this before.

DR. PINA: As Cindy just said, this is not our area of expertise, but I am amazed that we are tackling a syndrome that is so complex and so varied, where not only the mortality, but the morbidity may also be hinged upon the underlying pathologic process that gave the patient that ARDS in the first place. So I think our endpoints have to be different, because we are dealing with such a complex variety of syndromes ending up in this so-called ARDS.

I think the value of one of your trials was that the patients that were entered were very specific ARDS patients due to A, B, and C may help make the population a little bit more even.

I like the idea of the scoring system, because

with some other syndromes we have found that scoring systems of critical severity have managed to again, help us even out the population. For example, you showed in your study that the Apache score was higher than in perhaps the European trials, signifying that these patients were perhaps sicker.

So I think we may have to find scores that help us sort of put together all these different comorbid conditions. I don't think you can get away from looking at mortality, but it's such a complex disorder that I wonder if we should be looking at some other diseases, and not just ARDS.

DR. PACKER: We'll take one more question from Rob Califf. We're already behind schedule, and I apologize. I guess we could have the whole day on ARDS, and maybe or may not make any progress.

DR. CALIFF: My facetious comment is that using PO_2 would be almost as bad as using a blood pressure lowering endpoint for a disease where we're really concerned about whether people die or have strokes.

My serious comment is that I think it's important for people to recognize that the criteria for surrogate endpoint are not just that it's correlated with these outcomes, but that the difference, the treatment effect is explained by the difference in the surrogate measure. So there are many things that are correlated with disease

outcome which are totally uncorrelated with treatment effect, and should not be used as surrogate endpoints.

In fact, if you use these criteria, as was pointed out, there is almost nothing that really works as a surrogate endpoint by those criteria. I certainly think from what we've heard, PO_2 in this circumstance doesn't cut it.

DR. PACKER: For those who are joining this committee for the first time, one should not take strong encouragement to Rob Califf's first comments on his support for changes in PO_2. Rather, his comments should be interpreted as his lack of enthusiasm for blood pressure controls. Let's try to make sure that the message gets across faithfully.

Would that be accurate? Okay, good.

Why don't we continue with everyone's permission. It's probably a good idea to keep going. Does anyone want to take a break? A five minute break.

[Brief recess.]

DR. PACKER: What we will do now is proceed with this morning's session. We're going to be discussing neonatal respiratory failure.

Dr. Kinsella, please.

Agenda Item: Neonatal Respiratory Failure - Dr. Kinsella

DR. KINSELLA: I'm John Kinsella. I'm a neonatalogist at the University of Colorado and the Children's Hospital in Denver. I have been asked to speak today about the problem of hypoxemic respiratory failure and persistent pulmonary hypertension of the newborn.

This shows the overview of the talk. I'm going to begin with the definition of hypoxemic respiratory failure in PPHN. I'm going to describe how this problem of persistent pulmonary hypertension in the newborn can occur in association with lung disease, and talk about those categories of lung disease, including the meconium aspiration syndrome, respiratory distress syndrome, pneumonia, and lung hypoplasia, and those diseases predominantly affecting the lung tachypnea.

Also a subset of these patients who have primarily pulmonary vascular disease, and severe pulmonary hypertension, what we refer to as idiopathic persistent hypertension in newborns. And another subset of patients who have cardiac disease complicating their course in particular, because of left ventricular dysfunction and pulmonary edema hypertension.

I'll begin with a definition of hypoxemia, that is a relative deficiency of oxygen in arterial blood. In neonatology we often use an oxygenation index to assess the severity of the hypoxemia. That oxygenation index is

calculated using the fraction of inspired oxygen times the mean airway pressure on mechanical ventilation divided by the post-spectral(?) of PO_2.

In other words, this factors in not just the arterial PO_2 relative to avelolar(?) PO_2, but how much work it takes to get that particular PO_2. This is particularly useful in patients with significant parenchymal lung disease.

As just an example, an FiO_2 of 1 with a mean airway pressure of 20 cm of water divided by the post-spectral PO_2 gives an oxygenated index of 40, which Dr. Clark will talk about in the next talk, a common indication for progressive respiratory failure, a high risk of morbidity and mortality, and indication of a need for treatment with extracorporeal membrane oxygenation.

Respiratory failure simply indicates a need for mechanical ventilation. We just don't have a single definition. In general, clinical criteria in the newborn include: refractions, tachypnea, cyanosis or apnea with laboratory criteria, generally speaking including a increasing PCO_2 and falling PO_2, and an FiO_2 greater than 0.05. There is not a universally recognized definition for respiratory failure in newborns. The clinical impression of breathing and severity of disease plays an important role.

If we consider lung diseases which cause hypoxemic

respiratory failure in the newborns, although it clearly isn't as easy in the clinical setting, we tend to break these out into recognizable conditions, one of them meconium aspiration syndrome.

Others which are characterized by diffuse homogeneous tracheal(?) lung disease, for example respiratory distress syndrome and pneumonia, and in patients with pulmonary hypoplasia, which might be associated with oligohydramnios and compression of the lungs, or congenital diaphragmatic hernia. I will speak in a little more detail about each one of these, again, the purpose being to help us understand the kinds of diseases we are treating in newborns with newer therapies.

It is critical that we think about the causes of hypoxemia in neonatal lung disease. If you consider the intrapulmonary component, intrapulmonary shunting contributes to hypoxemia, which simply means that pulmonary arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lung.

Then of course ventilation profusion and equality and imbalance between ventilation and profusion, often referring to increased death state ventilation.

Shown schematically, we have areas of the lung which might have a normal ratio of ventilation profusion; others where that ratio is abnormal; still others where

there is atelectasis(?) and a shunting V/Q of zero. Certainly in this setting the arterial PO_2 is going to be related to that fraction of right ventricular output which passes through unventilated areas of the lung. So that intrapulmonary shunts, in many diseases causing hypoxemic respiratory failure in the newborn is important.

However, this slide shows the return of relatively low oxygen blood from the lungs, with little extra pulmonary shunting across the ductus arteriosus of the foramen ovale. In this setting we are going to advance the catheter into the left atrium of the pulmonary vein. It would be recognized that the predominant cause of hypoxemia in some babies is their intrapulmonary shunts.

It gets a little more complicated, because in the newborn there are open communications at the foramen ovale and the ductus arteriosus, contributing to extrapulmonary right-to-left shunting.

So in the newborn with these open communications at the foramen ovale and ductus arteriosus, pulmonary vasoconstriction can increase pulmonary vascular resistance, and allow that blood, when that resistance is super systemic, to cross right-to-left across the ductus arteriosus, and to cross right-to-left across the foramen ovale.

Now we can evaluate that in echocardiography,

looking at the direction of shunting at the foramen ovale and ductus arteriosus. One problem is that it's difficult to quantitate that. We also are limited in how much we can measure in intrapulmonary shunting because of these extrapulmonary shunts.

We can also of course measure the peak velocity of the regurgitation jet, and that's the right ventricular systolic pressure. So functionally, an elevated pulmonary vascular resistance is not so critical, but when it becomes super systemic we begin to have profound right-to-left shunting of the ductus and the foramen, causing critical hypoxemia in some newborns with persistent pulmonary hypertension.

We can't isolate with the pulmonary hypertension or the lung disease. We have to consider the relationship of the lung disease to pulmonary hypertension, recognizing that pulmonary vascular resistance increases at lung volumes above and below functional residual capacity. For example, underinflation in RDS can increase PVR. Overinflation in meconium aspirations can increase PVR in such settings. Extrapulmonary right-to-left shunting of the ductus and foramen can contribute to hypoxemia, and that's why this is a little more complicates. So extremes of lung volume contribute to the high PVR and extrapulmonary shunting.

Of course we have to consider cardiac performance

issues. Left ventricular dysfunction can cause mitral insufficiency, increase left atrial in diastolic pressure and pulmonary venous hypertension. In that setting, when that is the predominant cause of extrapulmonary right-to-left shunting and a high PVR, simply dilating the pulmonary circulation might not improve systemic oxygenation.

For example, in the setting with left ventricular dysfunction, there might be really relatively well oxygenated blood returning to the left atrium, but pulmonary venous hypertension contributed to pulmonary arterial hypertension and right-to-left shunting at the ductus arteriosus. So there are subsets of these patients who might have variable responses to selected pulmonary vasodilation.

If we define PPHN as a clinical syndrome associated with various lung diseases or idiopathic, associated with marked pulmonary hypertension and vasolability. Hypoxemia is caused by extrapulmonary right-to-left shunting at the foreman ovale and ductus arteriosus.

So when we think about PPHN, we have to think about the interactions. The underlying problem is right-to-left shunting of the ductus arteriosus and foreman ovale, which can cause critical hypoxemia. That is related to the relationship of pulmonary vascular resistance to systemic vascular resistance in the presence of the open channels,

including the ductus arteriosus.

So although we focus on the pulmonary vascular component of this disease, we can't ignore the fact that many of these babies have lung disease, with decreased lung volume, decreased compliance, and intrapulmonary shunting which contributes to hypercarbia and acidosis, worsening the pulmonary vasoconstriction, and comprising left ventricular performance, and affecting systemic vascular resistance. It is that interaction which makes that assessment a little more difficult.

Often when this occurs, it is a hard number to get at. I think Michelle Walsh-Sukys did probably the best job of analyzing the incidence of the problem. She did a prospective study of the incidence of PPHN which was defined by echocardiographic evidence of right-to-left or bidirectional shunting at the foreman ovale or the PDA.

Now that's important. We're not just talking about an elevated pulmonary vascular resistance, but the full consequences in the presence of an open foramen and a ductus of having a pulmonary vascular resistance that is high enough to allow for extrapulmonary venal/arterial mixture.

This was done on in born patients at 12 neonatal networks centers. She found an incidence of 1.9 per 1,000 births or 7,400 per year in the U.S. It's not a big

population of patients. We're not just talking about patients who are ventilated, but babies who have disease severe enough to call it PPHN.

Clinical presentation includes near-term or term incidence of hypoxemic respiratory failure, often with associated conditions of meconium aspiration syndrome, respiratory distress syndrome, sepsis and pneumonia, pulmonary hypoplasia, congenital diaphragmatic hernia, and then that relatively small subset of patients who have idiopathic PPHN, that is babies who have severe pulmonary vasoconstriction without other contributing factors.

Meconium aspiration syndrome is caused by aspiration of particulate meconium that causes a check style type obstruction, air trapping and perhaps surfactant inactivation. The most severe cases are likely to present in utero aspiration. The most common indication of the use of extracorporeal oxygenation of cardiopulmonary bypass in the United States.

As this is an example of a baby with meconium aspiration syndrome. Now this presentation radiographically is variable. Some patients have mild disease. Some have quite severe disease, associated with the particulate meconium which is in the periphery of the lungs.

Cranium staining of amniotic fluid occurs in 10-15 percent of pregnancies. Tom Wetzel's(?) observation was

that only 1 of 20 these develops the meconium aspiration syndrome we referred to.

It's also important to recognize that survival in the pre-ECMO era in patients with meconium aspiration and PPHN was quite low. In John Murphy in Boston he looked at the patients who had both meconium aspiration as a diagnosis and those who had PPHN. They had a very high mortality. In contrast, the cumulative survival for all cases of meconium aspiration with ECMO was 94 percent.

This slide is from Murphy's paper in 1984, showing the marked difference between a normal newborn who died non-pulmonary causes and a baby with meconium aspiration syndrome and PPHN. In the small arterial vessels in the lungs, showing striking muscularization of those vessels. So an anatomic or histologic correlate with severe pulmonary hypertension.

Now the condition is RDS or respiratory failure associated with surfactant deficiency or dysfunction. The pathologic diagnosis is highland membrane disease, or what we see under a microscope looking at the lungs is characterized by surfactant deficiency or dysfunction, epithelial injuries, and vascular protein leaks. The incidence is inversely related to gestational age.

This is a picture of a baby with respiratory distress syndrome showing the diffuse granularity and air

brocoframes(?) and underinflation, which characterizes this disease.

Pneumonia is associated with intra-amniotic infection or chorioamnionitis commonly caused by Groupi's(?) strep. It may initially be indistinguishable from RDS radiographically. For example, a baby with pneumonia, a baby with severe parenchymal lung disease in this setting. There are certain are problems with leaky matching and intrapulmonary shunting, but this is also a disease that not uncommonly is associated with severe pulmonary hypertension, and the other cause of hypoxemia, that extrapulmonary right-to-left shunt at the ductus and foreman.

Pulmonary hypoplasia can occur by external compression of the lung association with oligohydramnios. Perhaps renal disease and poor urine output is one cause, or amniotic fluid leak. There is high risk for air leak in pulmonary hypertension in this setting.

This is an example of baby with clear lung, but a small lung volume radiographically. Again, these patients often have pulmonary hypertension complicating their course.

In general, diaphragmatic hernia occurs in about 1 in 4,000 births. It is the most common on the left side. It is caused by herniation of the abdominal contents through post-suralateral(?) diaphragmatic defect. The worse cases are associated with compression.

In hypoplasia both the psilolateral and contralateral lung is often associated with severe pulmonary hypertension. Mortality remains high in this disease despite numerous interventions.

This an example of a baby with a diaphragmatic hernia compressing only the left, and potentially compromising the right lung as well.

Idiopathic PPHN is characterized by supra systemic pulmonary vascular resistance causing right-to-left shunting of the foreman ovale and/or the ductus arteriosus. It is not associated with other lung or systemic diseases. Again, it is characterized by clear lung fields on chest x-rays.

Now this is a disease which is associated with profound hypoxemia, but with little parenchymal lung disease. In this setting the extrapulmonary right-to-left shunting of the ductus and the foramen causes this baby's hypoxemia. One would expect that a selective pulmonary vasodilator would, by just dropping pulmonary vascular resistance and removing those extrapulmonary right-to-shunts, dramatically increase oxygenation.

Indeed, clinically many people have had that experience; have seen quite dramatic responses to selective pulmonary vasodilation with inhaled NO. Again, this represents a relatively small subset of the patients we treat. This is the only population that was treated with

inhaled nitric oxide. We see striking differences between them with a small number of patients.

The problem is we much more commonly see babies like this, who have severe lung disease, which complicates the course. In this setting, with air space disease, in this case associated with pneumonia, and inhalational dilator might not be expected to be quite as effective. This baby certainly can have pulmonary hypertension.

Again, we can't just consider the pulmonary vascular component. It's a more complicated problem than that. Certainly babies have maladaptation or arterial muscularization or hypoplasia, causing the pulmonary vascular component to be critically important when evaluating the disease, but they also have lung disease that more frequently complicated the course associated with meconium aspiration or pneumonia or surfactant deficiency and RDS.

Again, compromised cardiac performance can occur with hypoxic ischemic injury, electrolyte abnormalities, sepsis, and RV pressure overload. It's the interaction of all of these therapies that makes this a challenging disease to manage.

As Dr. Zapol showed this morning, there was some early experience that the acute response to inhaled nitric oxide and more prolonged exposure to NO. It is important to

point out though that in this set of patients we had tried to optimize lung inflation with other interventions, in particular a different kind of ventilator device, the high frequency oscillatory ventilator, which is used to help recruit and sustain lung volume without the potential injury caused by large vaso pressure changes on tidal volume conventional ventilation.

After having done all of those things and trying to optimize lung recruitment, we then added the nitric oxide and saw consistent and sustained responses.

Let me show you a couple of examples, because I think what I've been asked to do is to talk about the physiology of this problem. I'm going to show the application of different therapies, including high frequency oscillation.

This is a baby with a diaphragmatic hernia. High frequency oscillation, which is used to recruit this lung; make it look more like that. Then inhaled nitric oxide is used specifically to cause selective pulmonary vasodilation. There are going to be some examples, but I think it helps teach us about the nature of the pathophysiology of each individual patient.

This shows the changes in PO_2 in that baby on conventional ventilation in the previous slide, with a poorly inflated right lung. Now this baby already has a

very small left lung, and a small cross-sectional area of lung, across which right ventricular output will flow. So some measure of a fixed high PVR, on top of that reactive pulmonary hypertension which causes hypoxemia by the right-to-left extrapulmonary shunting. Certainly, this baby has some measure of intrapulmonary shunting as well.

The baby was treated with nitric oxide, so the transient increase in PO_2, which was not sustained on conventional ventilation. We then switched to high frequency oscillation, the goal again being to recruit that atylacatic(?) lung. That treatment by itself showed no improvement in oxygenation, but we did do a better job of inflating the lung.

After having done that, we again gave a trial of that inhaled vasodilator assuming that now with a better lung inflation, that inhalational dilator might be more effective, and indeed, that's just what we saw. After a brief period of high frequency oscillation recruiting the lung, adding the nitric oxide back, we saw a marked and sustained improvement in oxygenation.

So what we are trying to do, at least with trying to understand the underlying physiology in these patients is say we have two important factors that contribute to hypoxemia, the lung disease, causing intrapulmonary shunting, and the extrapulmonary right-to-left shunt

associated with pulmonary hypertension.

As tools one used to recruit and sustain the lung, and the other used to cause selective pulmonary vasodilation, we were able in some of these cases to tease out the relative contribution of the pulmonary hypertension and the lung disease.

Another example is a baby with severe parenchymal lung disease before and after treatment with high frequency oscillation. Now there are other therapies, other ventilator devices or strategies that might have the same effect. We have experience with this particular device, and that's why I'm showing its effect, because it seems to be quite effective in inflating the lung that is very stiff on conventional ventilation. It offers us the opportunity to change the nature of the underlying lung disease as we assess the response to different interventions.

This shows this baby's response to different interventions. This baby had a right-to-left ductus arteriosus shunt. The pulmonary vascular resistance is supra systemic. The PO_2 is about 20. We treated this baby with nitric oxide and in this setting actually pulmonary vascular resistance fell and the ductus reversed its direction and it was now left-to-right.

In other words, that extrapulmonary component went away. The nitric oxide did exactly what we asked it to do.

It dropped the PDR, but now we have PO_2 of 40 without an extrapulmonary shunt. What it did was unmasked the severity of the underlying lung disease in this particular case. Recognizing then that this is predominant parenchymal lung disease and intrapulmonary shunting giving us a PO_2 of 40 and 100 percent inspired oxygen, then we addressed the underlying lung disease with high frequency oscillation and with that alone saw continued improvement in PO_2.

So the interaction of these things, the pulmonary hypertension and the parenchymal lung disease is vital to understanding the role of these new therapies.

We then used that early experience to ask a study, and this wasn't a placebo controlled trial or one that was designed or powered to look at the reduction of ECMO. What we wanted to do was learn more about this disease of PPHN and hypoxemic respiratory failure, and how these new therapies might be applied.

We sought to determine the ability to sustain oxygenation in babies with severe PPHN. We defined that by echocardiagraphic evidence of extrapulmonary right-to-left shunting. Look at their response to inhaled nitric oxide as a selective pulmonary vasodilator on conventional ventilation, the ventilation strategy they were on.

We randomized these patients after stratifying them into different categories -- meconium aspiration or RDS

-- to either getting inhaled nitric oxide added to the conventional ventilator, or switching to high frequency oscillation.

Babies who failed treatment with either one of these would be offered the other treatment, and failing both, we combined them reasoning that in some patients who had both lung disease and pulmonary hypertension, the combination of the therapy designed to inflate the lung, and the therapy designed to selectively drop their PVR, we might see added benefit.

We had 205 patients in this study. It was a multi-center trial with term babies; 39 went to gestation at 3 kilos who were quite severely ill. The oxygenation index was 48. Other values an AE(?) ratio of 0.06, a PO_2 of 42 and 100 percent oxygen. So these obviously were quite sick babies.

Now this slide just shows the initial randomization. The babies in each category were randomized within that category. We meant to ask the question, what percentage of those babies given one intervention, would respond? That is, they would recover without the need for cardiopulmonary bypass.

Now many of these patients failed that initial assignment and were crossed over to the other therapy. This just shows their response to initial assignment. What

really I think jumps out at you in this slide is that without significant parenchymal lung disease, they had a very different response to inhaled nitric oxide compared to treatment with high frequency oscillation, a much higher response rate.

These are small numbers. It wasn't hard to find a difference. There isn't one there, but the trend you can see might be very different depending on what the underlying lung disease is. In some patients with severe parenchymal lung disease their response might be better to high frequency oscillation than selective pulmonary vasodilation.

So we can't lump all of these babies together and say a newborn is a newborn. We have to think about the underlying pathophysiology, because indeed the physiology matters.

This is a different take on it. This is a group of babies who were treated initially with conventional ventilation and had nitric oxide added. It shows their PO_2 over two hours. These are babies who did not have a sustained improvement and failed that therapy. They then crossed to the alternative therapy, which was high frequency oscillation; on average a slight increase that wasn't sustained.

Then going back to the baseline, we took this response and added nitric oxide to it. This was the mean

response of babies failing both of those interventions, showing a progressive improvement, and interaction between the lung recruitment therapy and a selective pulmonary vasodilator.

This summarizes the results of that trial. Again for meconium aspiration, respiratory distress syndrome, and patients without significant parenchymal lung disease. In this setting the combination of these therapies, one, is doing something very different than pulmonary vasodilation, trying to recruit and sustain lung volume. A far greater percentage of responders are both meconium aspiration and RDS than either intervention alone.

Now it's important to recognize that these are babies who failed both of the other therapies. Combining them has a higher response rate nonetheless than the individual treatments alone. In patients without significant parenchymal lung disease the response rate to high frequency was quite low. The response rate to nitric oxide during conventional ventilation was significantly better. Treating with high frequency oscillation and nitric oxide wasn't any better than INO alone in that group.

So there are multiple pathophysiologic processes that contribute to hypoxemia in the newborn. Therapies must target the specific underlying disease process. PPHN can complicate all of the respiratory diseases caused by

hypoxemic respiratory failure.

It is interesting that if one just looks at that subset of patients with parenchymal lung disease, but has this problem fairly unique in the newborn, with open ductus arteriosus and foramen ovale, passages that cross with blood can cross right-to-left, causing venal arterial mixtures with supra systemic PVR. Dropping that pulmonary vascular resistance even slightly can cause a dramatic improvement in oxygenation.

It gets a little more complicated when you begin to look at the other diseases that contribute to lung disease in newborns.

So low dose inhaled nitric oxide causes sustained pulmonary vasodilation, but the efficacy may be limited by ineffective delivery, for example severe lung disease and underinflation, and certainly compromised cardiac performance adds another wrinkle to the equation, which makes this a complicated problem.

I will end by saying that in patients with lung disease and PPHN lung recruitment strategies augment the response to this inhalational vasodilator.

I'll stop there.

[Applause.]

DR. CLARK: My name is Reese Clark, and I'm a neonatalogist at Duke University Medical Center in Durham,

North Carolina. My task this morning is to discuss some of the other therapies. Originally I had planned to talk a little bit about lung recruitment, but as John and I discussed these presentations, that fed in much better with his presentation to try to dissect the pathophysiology. So I'll focus primarily on the randomized controlled trials that have been done in this subset of patients, as well as discussing the issues of ECMO and its role in the management of these patients.

There are a whole host of therapies that are involved in caring for these critically ill infants that are referred to our institutions for a variety of different supports. Mechanical ventilation is rapidly evolving. Just five years ago most of us were not using this type of control devices in the neonatal unit, because we didn't have the technology to really sense and deliver a synchronized breath. Over the past five years most institutions are using this relatively commonly.

High frequency ventilation is delivered in a variety of different modes -- high frequency jet ventilation, oscillation, and flow interruption are all different techniques that can applied to these patients.

In addition to different modes of assisted ventilation, we have access to a variety of different drugs and other rescue tools. Surfactant has been used in a

randomized fashion, and we'll talk about its use as a rescue tool after respiratory failure, as well as established.

There is a small study looking at surfactant as a prophylactic tool to try to prevent the evolution of lung disease in these critically ill patients, especially with meconium aspiration syndrome. There is a emerging trial looking at KL4 as a method of surfactant lavage to remove some of the meconium.

Alkalosis has been used. It has fallen out of favor as a result of the issues that go along with decreased cerebral blood flow, as well as how you get the alkalosis, whether you infuse carbonate, or make a patient alkalotic by driving their CO_2 down. There are consequences to those therapies.

Vasopressors to support craic(?) output are important. We'll hear a lot about nitric oxide. Intratracheal pulmonary ventilation, where gas is actually delivered to the trachea to try to reduce dead space ventilation and improve ventilation at lower tidal volume deliver.

Liquid ventilation is still out there and is again preparing to be studied in a randomized controlled trial.

If all of these things fail, then we are offering ECMO. How ECMO is offered in the United States will be the topic of the next group of slides, and can be done in a

variety of different methods. The goal of each of these therapies really is to optimize oxygen delivery. That is not equivalent to changes in PO_2, but reflects delivery of that oxygen by hemoglobin and cardiac output to tissue.

Carbon dioxide removal is equally important. In the process of managing these babies, our goal is to avoid propagation of lung injury and promote normal recovery. It is critically important to realize that in the newborn we have a tremendous opportunity, because most of these patients will get better over a five to six period if we do not cause irreversible lung injury. The complications of multi-system failures that we see in ARDS are not as common in the newborn.

As John has very clearly outlined, targeting the therapies is critically important as we manage these neonates that have very diverse types of illnesses. We must identify the primary pathophysiology, and this can be quite difficult, and can take some time to sort out.

As we are sorting out these underlying problems, we are assessing therapeutic interventions that help us identify the underlying pathophysiology. Waiting for that response can delay the initiation of the definitive therapy. Obviously, if we delay the definitive therapy too long, efficacy, like immunizations is not as good.

If we consider that we target the pathophysiology

and try to reverse the underlying problems, and we recognize synergistic effects, then we can find that there are therapies that would allow us to offer excellent care these patients.

Nitric oxide is primarily targeted to opening vessels and improvement ventilation profusion matching. Surfactant, high frequency, prone positioning, and a variety of other things have been targeted at improving lung inflation, and avoiding volume trauma if you will, large tidal volume breaths.

To further kind of detail my schematic of how I approach these patients, is the primary pathophysiology is atelectasis. These therapies might be helpful. Lung maturity we have certainly seen in randomized controlled trials that surfactant in a premature baby, improves gas exchange and outcome. High frequency ventilation has also been studied in these premature babies, and appears to have an effect.

If the problem is gas trapping, then we have to use a different approach to ventilation and begin to slow the rate down, shorten the inventory(?) time and allow for adequate gas exit from the lung.

Pulmonary vasodilators are targeted at improving pulmonary vascular resistance, and cardiotonic agents improve cardiac function. Antibiotics help us with

infection.

So with the concept that there are many therapies out there vying for the management of these babies, let's look at the N therapy, and ask the question, is that therapy a beneficial therapy in neonates with critically hypoxemia?

First of all, let's orient to what ECMO is. There are two different forms that are commonly employed. This is the veno-arterial where the carotid artery is ligated and blood is returned to this site. The jugular vein acts as the drainage site where blood is pumped outside of the baby's body, oxygenated in the membrane lung, rewarmed, and then redelivered to the carotid artery.

Over the last five years there has been an increased use in newborns of double lumen cannula, where the blood is both suctioned out and returned to the right atrium with a veno-venous cannula. This obviously decreases the need for carotid ligation, which most of us believe is important.

This is just a picture, to give you a sense of how this is done, and to impress upon you that obviously these cannulas, and positioning these cannulas is critically important, and obviously when those cannulas get disturbed or positioned in the wrong way, that is a life threatening event.

How often is ECMO used in this country? There are

111 centers that report data to the ELSO registry on standardized data collection sheets. Since 1986, there have been about 13,000 babies that have been reported to this registry. The average time on ECMO is about 135 hours. If we take the diaphragmatic hernia patients out, it comes closer to more like 100 hours.

Overall survival rate in these patients is 79 percent. If we look at patients without congenital diaphragmatic hernia, the overall survival is about 86 percent. Despite more and more interest in ECMO, about only 25 percent of the patients are treated with this particular mode of therapy.

The diagnostic categories have changed over the last several years as we look at epidemiology of patients treated with ECMO. So that if we look at the number of babies that are defined with RDS, that number is shrinking, in my mind most likely due to the introduction of surfactant.

The number of meconium aspiration syndrome patients that make up the relative mix has also appeared to have decreased some. The PPHN group is still out there, and the diaphragmatic hernia is making up a larger and larger percent of the total patients. This is important as we look at the outcome of these babies over time, because obviously if you have more of your mix being congenital diaphragmatic

hernia, you can imagine that the mortality statistics of patients treated with ECMO would increase, because the rescusable nature of that disease is different.

As Dr. Zapol suggested, the need for ECMO is being reduced. The 1997 data may not all be reported yet, but the overall trend is a decreased utilization of ECMO in the United States.

The survival rate is very diagnostic-specific, with most institutions taking care of meconium aspiration syndrome having a success rate close to 96 percent. RDS drops down some, and obviously the worse survival is in patients who have congenital diaphragmatic hernia.

If we look at the outcomes of babies over the couple of years and ask are we doing better in the patients with ECMO, or are our numbers changing if we look at overall mortality, there is an increasing mortality, but when you correct it for the number of patients who have diaphragmatic hernia, and look at just the non-diaphragmatic hernia patients, the trend is not as striking.

If we look at chronic lung disease as defined as oxygen needed at 30 days, the rate is pretty flat. The occurrence of intracranial hemorrhage being about 12-15 percent. It continues to be pretty stable.

Well, if we are using this in this country, what are the data to suggest that this therapy actually saves

life and promotes normal outcome? I think the best data on this actually come out of the United Kingdom in a large multi-center trial, although there were two trials done in the United States prior to this trial which pretty much showed that it was effective, and we will go with this large trial.

Between 1993 and 1995, 185 patients from 55 centers enrolled in this randomized controlled trial. The gestational age had to be greater than or equal to 35 weeks, greater than 2 kilos. As John suggested, they had to have severe respiratory failure as defined by an oxygenation index greater than or equal to 4.

The patients who were randomized to ECMO were transported to five ECMO centers. The non-ECMO patients stayed at the original center, and received conventional management at that center.

The alternative therapies that were available in this study, surfactant was used about 37 percent of the time. High frequency and nitric oxide were used about 20 percent of the time in this trial. We will look at some of these uses in other studies as go through here. The important aspect is, as you might imagine, there was some imbalance in the use of these therapies, though they weren't statistically different with the control limb more often receiving the alternate therapies.

Recruitment was stopped in 1995 by the steering committee on advice of an independent data monitoring committee based on the results that are reported here. Survival or the death rate of patients assigned to ECMO was 32 percent as compared to 54 percent in patients who received conventional management.

There just appeared the one year follow-up data. I'll kind of update this, but basically the one year follow-up data was published in the electronic pages of Pediatrics last week verifies this slide, which is that survival applied irrespective of primary diagnosis, disease severity, or type of referral center. Survival without disability at one year was also better in patients treated with ECMO.

Said a different way, the number of handicapped children showing up at one year of age in the survivors was no different between the two groups, but there were a whole lot more survivors in the ECMO group. So the number of patients showing up well and healthy in patients who were offered ECMO compared to conventional management.

These are the diagnostic-specific outcomes showing that in each of the diagnostic categories, ECMO showed a dramatic improvement in the survival rates, so that independent of the underlying diagnosis ECMO is beneficial at promoting intact one year survival.

Now there has been the question raised as to

whether ECMO has been adequately studied in the United States. I'll show this slide for dramatic effect. This appeared in The Boston Globe in August 1989 after Dr. O'Rouke(?) had completed a trial in the United States looking at ECMO. This is considered by most of us to be the defining study that ECMO is actually beneficial, and led to the more widespread and careful use of that process.

It reminds us that the public is very interested in these types of issues, and that we can, looking at mortality endpoints in newborns, get into situations where we are faulted for limiting life saving treatments.

So why should we avoid ECMO? If ECMO is a life saving therapy that promotes survival, what should make us want to avoid this therapy? Well, still we're only looking at a 25 percent utilization rate for baby ECMO. That means that the carotid artery is ligated. I think that the long-term consequence of carotid artery ligation are yet to be known, because ECMO survivors are still young, and we know that as they grow older, we have not hurt these patients in any way is not clear.

In fact, there was some data presented in the ECMO meetings that suggest that the long-term follow-up needs to go on for years and years before we can certain that these children are actually doing perfectly well.

Exposure to twice the neonates total blood volume

increases the risk of transmission of hepatitis and HIV and a lot of these other diseases that we are probably yet to know. Certainly the bleeding and infection risks are very real and common in these babies.

These are the mechanical complications and the frequency as reported to the ELSO registry. It gives you a sense that these problems are not infrequency. Obviously clots in the circuit here can be life threatening issues.

If we look at the occurrence of bad things in the patients, infarcts(?) and bleeding in the brain, which in part be related to what happens to the baby before they get to ECMO. Again, delaying ECMO until the time that the patient actually has a life threatening event may increase the risk, or certainly does in retrospective analysis. There is a very real potential for injury in all of these particular areas, including renal dysfunction.

If we look at the yearly cost of an ECMO program as estimated in the most recent text on ECMO, it's about $300,000 a year to run that. The estimated cost per neonatal patient is about $20,000.

Dr. Adler has provided me with some data from Atlanta looking at the approximated cost saving per year over the last three years at his institution by using nitric oxide, at an estimated cost savings of about $90,000 per year, while his delivery service has gone up by from $8,500

to $12,500. His ECMO, the full rate has gone from 7 patients on average per year to about 3 patients per year.

I'm certain that there are other therapies that they have introduced that have helped with this group, but certainly there is probably a cost saving that can be occurred if you less than invasive tools.

Well, what other trials are there in this group of patients, and what endpoints have they looked at? Without exception, randomized control trials in this group of patients with severe respiratory failure at term has looked at ECMO as their primary outcome measure, or the avoidance of ECMO, more precisely stated.

This is a randomized controlled trial. It took several years to complete. There were 44 sites. This is randomized trial, and I wanted to impress upon you 44 sites over a 3 year period. They had 328 patients that met these criteria. So trying to get an earlier treatment to these patients who aren't as critically ill as actually needing ECMO.

There were no differences in the complication rates in the surfactant treated compared to control infants or airway or chronic lung disease, severe intracranial hemorrhage were similar in both groups.

The patients who were treated with surfactant less often needed ECMO than those treated with the placebo at 29

versus 40 percent.

Again, to bring out the issue that it is the diagnosis or the underlying pathophysiology which determines the most benefit, the patients who appeared in this post hoc(?) analysis to derive the most benefit from this intervention, were patients with meconium aspiration syndrome. Patients with PPHN were not as likely to benefit. In fact, there was no evidence of benefit for those patients. This is the group of patients that John talks about as probably most likely to benefit from inhaled nitric oxide.

There is a much smaller randomized controlled trial looking at surfactant as a prophylactic to prevent the evolution of meconium aspiration syndrome. It was done by Dr. Findlay. This is a randomized, single center study that involved 40 patients. There were trying to treat patients within the first six hours of life, and surfactant was given over a 20 minute period through a side forty(?) batcher.

Again, there appears to be a benefit. This trial is woefully underpowered to look at any safety issues, but they did begin to suggest that with regard to things like need for ECMO and hospital days, that there might be a beneficial effect.

Now we have tried to get interest in reproducing this trial. Most of the neonatalogists in the country feel

like the surfactant has been shown adequately based on these data to be used in all patients, and we have not been successful in mobilizing any interest in a randomized controlled trial of prophylactic surfactant. A surfactant wide trial is being organized by Dr. Tom Luzeral(?).

This is just a summary of the different data that are out there, using in randomized controlled trial fashion the avoidance of ECMO. This is the prophylactic trial that we just went over. This is the term infant trial. These are the neonates you will see in greater detail. This is Dr. Robert's data, you will also see in detail, percent need for ECMO control versus treatment. You can see an effect in each of these.

So that our issues with regard to things like high frequency ventilation and surfactant and other modes of ventilation, there is a question now from us as to which therapy do we use when, and which one should be targeted at which particular disease state. I think identifying the underlying pathophysiology is a key to that endeavor.

To give just a scent of how often these alternate therapies are used in the United States, the NINOS trial, high frequency ventilation was used in 55 percent of the patients; 71 percent of the patients received surfactant; and 10 percent of the patients received neither one of these therapies.

I want to conclude with a group of slides talking about where are we headed with this issue, and what kinds of things are realistic to try to state. Just to remind you, the NINOS study showed an impressive difference in the need for ECMO among patients who were offered nitric oxide as compared to control. The combined endpoint of death by 420 days or need for ECMO was also highly statistically different.

So we can ask the question is mortality lower in nitric oxide? The point estimates would suggest yes, from this large trial, but it's not statistically different, and the P value is 0.6. So there is a 60 percent change that this difference is purely random.

I asked our statisticians to go back and define how many patients we actually needed to prove that the mortality improvement seen with nitric oxide was real. This is the estimated number of patients that would be needed for that particular trial.

I think the second question that we have asked in the ARDS model and has to be asked in the neonatal is how many of these deaths could actually be assumed to recoverable if we had a perfect pulmonary vasodilator that would allow the lung to open. In other words is the surrogate marker attached to the treatment or are they unrelated to each other?

If we look at the Eckelson(?) data between 1991 and 1998 -- this is the ECMO program I ran down in Emery, we had 150 patients that were neonates; 27 of these babies died. If we look at diagnosis-specific survival rates, the meconium aspiration, 96 percent survival; only 4 percent died. Most of the patients that were dying were actually patients with diaphragmatic hernia.

If we look at the causes of death that were reported in the charts, these are the causes of death: congenital diaphragmatic hernia; severe brain injury; multiple organ failure; congenital heart disease; lung hypoplasia; and adeno virus; alveolar capillary dysplasia, which even though it responds to initially to nitric oxide, at least in the reported data to date, it looks almost uniformly fatal.

Diaphragmatic hernia, the randomized controlled trial in that, the patients did not show a benefit to the early use of nitric oxide in the those groups of babies that was reported by Dr. Conrad(?) at the neonatal network. So that our recoverability or the prevention of death in this group of babies is not likely to be dramatically improved.

So that if you use ECMO as a rescue tool, it evens the playing field for any therapy that is used prior to ECMO, unless that therapy delays the institution of ECMO to a point that the patient is no longer recoverable. From my

both of the speakers, Dr. Kinsella and Dr. Clark. Let me in doing so, ask the committee specifically to ask questions about pathophysiology, and about the use of ECMO. Let me ask the committee to reserve until after the lunch break, a discussion about Dr. Clark's position on ECMO as a surrogate marker for outcome. I ask the committee not to talk about that now. Talk about it after the break.

DR. RODEN: Those were two really excellent talks that helped me put things into perspective. The talks raised a couple of questions in my mind which some of the comments before the break also raised. I would just like to have some discussion from someone who knows something about the issue of subsets.

We heard this morning that inhaled nitric oxide may be a longer therapy for specific subsets -- the donor transplant group, the lung transplant group. You have the data in the kids that there may be subset-specific responses to disease.

I'm an arrhythmia doctor. I think that if someone came to the agency and said I have a drug to treat arrhythmia, the agency would laugh at them, and would want to say, which kind of arrhythmia. So I think you may be in the same position.

You have identified specific subsets of patients in whom there would be a dramatic readily ascertainable

response to nitric oxide. I'd like you to talk about those.

I was particularly intrigued by the lung transplant. It sounded like it ought to be pretty straightforward to me. I have a single site study in at Washington University in lung transplant, and answer this question.

DR. CLARK: The answer to your question is that clearly the subset analyses and some of these analyses have been done post hoc, but over and over again the trend is that the group of patients who clearly benefit the most with nitric oxide are those with relatively minimal lung disease, but profound pulmonary vascular constriction. They have the most physiologic response. They have the least need for ECMOs and alternate therapy.

They seem to be least responders to other things like surfactants and high frequency ventilation. The problem is that the number of those patients is relatively small when compared to meconium aspiration syndrome or diaphragmatic hernias. So mounting a study that would just look at that group of patients would again, be a very difficult study to do, because the numbers are so small.

DR. GOLDSMITH: Part of the problem is that the only have the subsets by diagnosis, and we don't have by run biopsy until autopsy, if that occurs. If you look at it was Walsh-Sukys who originally made some of the pathophysiologic

distinctions of looking at the group of babies with PPHN, one with a normal number and structure of their pulmonary arteries, and the other with an abnormal number.

Of that group, the ones with the normal numbers, some of them have vascular remodeling. We don't know that when we start. Some of the have probably some inequality between vasodilators and vasoconstrictors, and we don't know which one was quite there.

We can take a look at the clinical diagnosis. Like for example in meconium aspirations that we do very well with, with ECMO, it may be more of a vascular remodeling problem from the in utero subclinical hypoxia over days more than the aspiration problem itself.

So generally, we are finding that INO is given the whole group, with probably the one caveat that we don't have good statistics on in terms congenital diaphragmatic hernia. Some of these represent an imbalance between vasoconstrictors and vasodilators, and hoping that there is not a lot of vascular remodeling.

DR. LINDENFELD: Can you tell me how can you use an oxygenation index as part of your outcome, and is there a linear correlation with that and outcome?

DR. CLARK: The oxygenation index, there was a whole tremendous group of papers that came out in the late 1980s that questioned the use of that particular number as a

way to deciding the exact amount, and that was used to look at mortality rates.

But even in the best situation, mortality rates associated with the patient and pulmonary hypertension and an oxygenation index of greater than 45, more than 50 percent of those kids are going to die. Yes, it wasn't 80 percent mortality is what Dr. Bartlett had suggested; it was still high.

Is the oxygenation index an adequate surrogate marker for a bad outcome? Probably not. The oxygenation index as the only thing that goes into deciding who needs ECMO and that's absolutely not true. In fact, if you look at the registry, there are a lot of other reasons patients are placed on ECMO. One of the more common ones is failure of maximal medical therapy. This gets to the issue that we're going to discuss after lunch, so I'll stop there, which is how do you decide somebody needs ECMO.

DR. LINDENFELD: Another question I had we talked a little bit before about inhaled nitric oxide providing blood flow to well ventilated sections. Does it actually do that by taking blood flow away from other sections, or does it increase total blood flow?

I guess the second question, if decreases blood flow to poorly ventilated sections, is there a consequence to that?

DR. KINSELLA: Well, that would also depend on what overall pulmonary vascular resistance is. In a newborn there might even be bypass of the lung. Simply dropping pulmonary vascular resistance would have both effects. We think that at low doses we have a micro selective effect in the lung that Dr. Zapol spoke about, but overall pulmonary vasodilation should increase blood to the lungs by reducing that.

If that is case, then you are selectively directing flow to better ventilated units, then overall the fraction of right ventricular openings passing through unventilated segments is relatively lower. So I guess it would have both effects.

DR. LINDENFELD: Just in the ARDS, where an issue of stealing is perhaps a horrible thing. I wonder if don't have a model to present a consequence to that? In other words, it's taking blood flow away from the poorer ventilated section results in --

DR. KINSELLA: Results in what?

DR. LINDENFELD: Let me just correct my language. If you steal blood from a better ventilated section and the total blood flow is not increased, and you lower to poorer ventilated sections?

DR. CLARK: There are several basic experiments in neonates that would suggest that it's probably not true.

John's own data would suggest an overall lung benefit from using nitric oxide in a disease process where there is different pulmonary vascular resistances. It doesn't appear to be where you have blood being pulled away from certain areas of the lung and that causing injury.

In fact, ECMO is probably another experiment in that regard. If go on VA ECMO and you pull a nice(?) one out of the right side of the heart, then you have dropped pulmonary artery flow to that lung, and that doesn't appear to cause lung injury.

DR. LIPICKY: I would like to just pursue the thing of how you make the decision to go to ECMO. Let me say that I would provide you with my expert opinion that this baby has trouble with oxygenation, but I could deny you any knowledge of what the level of PO_2 is, and I would not allow you to look at the baby's skin color or the color of the blood. Would you be able to make a decision with respect to whether or not you place the baby on ECMO?

DR. CLARK: I think that the reality is that when you ask me how I decide, I would decide how much lung injury is there. I would look at the clinical course that the child has been through, and how old is the child. Do I know how much oxygen is -- I don't know that either probably.

His point is that without knowing what the oxygenation is, you can't really make a decision about

whether a patient should go on ECMO.

DR. LIPICKY: I was just trying to find out whether that's true or not, because I would suggest that you can. That it's nothing more than a measure of PO_2. Therefore, it doesn't mean anything unless you measure PO_2.

DR. PACKER: I thought I heard -- just maybe I heard a misstatement -- that we were going to have a discussion after lunch on whether a patient should go on ECMO. Is that correct?

DR. CLARK: Yes.

DR. PACKER: Since it seems to be somehow formally developed into the program, maybe it would be a good idea to hold that, because otherwise we're going to be discussing something with necessarily having heard all of the data that pertains to it.

DR. THOMDONI: You mentioned that VV ECMO is not compared carotid ligation. Is it because it's difficult to do, or it is taking time to accept? Because one of the things you are emphasizing is the carotid ligation might be bad for you in the long run, but in a baby that doesn't pose a problem. You can even save a child's life for $20,000; that's not too much price to pay when we spend so much time on terminal illnesses at the end of life.

How can you deny that you can save a life with a procedure which is so simple? So can you give me some idea

really why it's not popular? Is it technically difficult?

DR. CLARK: First, let me agree with you that the cost piece is the last thing that we really need to worry a whole lot about, unless we can show all the other things are equally -- that the outcome is equal. Then cost does become an issue.

The issue of VV ECMO, I can't explain that. I can tell you that at Emery University where we were running the ECMO program there, that 90 percent of the patients we treated were treated with VV ECMO. A lot of this is an educational piece, and while there has been an increase in the use of VV ECMO, it is an order of magnitude more difficult to manage because of the gas exchange differences.

So the ECMO community is clearly trying to change that, and there are probably people here who can address that probably even better than myself.

DR. THOMDONI: I think that's a very valid issue. Another issue is to my knowledge with the British study ECMO definitely saves lives. How one could deny that -- the patient needs that, he needs it. How can you withhold it even for a day or two? The question is in the count you are showing, how many people have actually died because of the lack of application of ECMO early on?

DR. PACKER: Let's hold the question, because we can't address that until we discuss the studies in the

context that we would interpret --

DR. KINSELLA: I just want to address that for a second, because I think that's it probably inappropriate for us to look at these data to say, it seems like a good idea and venous ECMO is probably the way to go. That's not the purpose of this meeting. The reality is as fewer patients are treated with ECMO in this country, the onset of other kinds of approaches that might be technically more difficult are much less likely to happen.

That's really not the point. What we presented was what we did. I think that's important.

DR. THOMDONI: Does this mean more patients are dying because you are not doing that?

DR. KINSELLA: I don't think we have any evidence of that.

DR. MARIN: Rick Marin. I'm chief of pediatrics at State University in New York and Children's Hospital. I have a comment that relates to the question of decreasing blood flow and steal and injury to the lung. The minute before birth the blood flow to the lung is increased by 90 percent from what it is the minute after birth. This points out a basic fact. Children are not little adults.

That statement is obvious to everybody in the audience who is a pediatrician and takes care of children, because it is a fact on which the specialty of pediatrics is

filled. It is very important to consider when you are looking at the effect of the pharmacologic agent in the neonate.

The human neonate responds to pharmacologic agents more like the neonate of other species than it does like the adult human. Two good examples of that is surfactant therapy. The neonate with respiratory distress syndrome responds dramatically with increase of PO_2 and increase in survival with surfactant. Adult with respiratory distress syndrome does not.

In a neonate with respiratory failure has an improvement in survival with ECMO, the adult does not. It is unlikely that the response to inhaled nitric oxide by a neonate with isolated failure of the lung, and whose only or a major of pathophysiology is lung failure is pulmonary vasospasm, his response is not likely to look much at all like that of the adult with multi-organ failure, and whose lung failure of those multi organs is only a small part of pathophysiology.

The FDA has either recently promulgated regulations rewarding pharmaceutical companies for testing established drugs on children, and requiring them to test new drugs on children for approval. They have done this because of the recognition that it is hazardous to extrapolate toxic or therapeutic effects from the adult to

the newborn. Children are not little adults.

[Applause.]

DR. PINA: For my own education, how does high frequency oscillatory ventilation recruit other areas of the lung, and could you give us a brief explanation? It seems like that is becoming more often used. I got the gist from the presentation that you felt that that had impacted significantly on a lot of these children.

DR. KINSELLA: It doesn't do anything by itself. There is nothing magical about this device. The idea is that by using an appropriate recruit in pressure, and by that I mean a mean airway pressure. The big difference between that device and a breath is that a lung can be recruited with a high mean airway pressure without the increase in peak pressure and large basic volume change that we believe injures the lung. That has been demonstrated now for some time in various animal models, and that's pretty convincing.

That is only effective though if one recognizes that the recruitable lung volume appreciates. What happens on a pressure volume history is this curve, it uses the device to begin to open the lung up. So it is as much technique and strength as it is the device. Don't get me wrong. There are other devices and strategies and other kinds of approaches that might do the same.

The point of it is it's something we have used to recruit the lung, and using that as tool, combining that with selective pulmonary vasodilation helps us understand the underlying disease.

DR. PACKER: We only have time for one more comment, but before doing that I guess I just want to clarify, it isn't clear from the schedule when the issue of indications for ECMO were going to be discussed. There is no separate presentation on that. Did you say it was scheduled for this afternoon?

DR. CLARK: No, I thought you said you were going the raise question.

DR. PACKER: Okay, fine. That's terrific. We'll take one more question.

PARTICIPANT: I think it's important that the members of the committee understand that pulmonary hypertension, because 97 percent of the babies with this disease present by 72 hours of age, they are pretty frail and unstable. Making the trials of the various therapies in this patients has not been successful.

By the end of today the committee will have seen the entire body of literature of randomized trials available in this population. And these newer therapies, like inhaled nitric oxide are not supplanting other therapies. They are being used in addition to the existing therapies, usually in

off label indications.

So in the NICHD observational work, the mean number of treatments received by each patient was 4.5, and that was before inhaled nitric oxide or surfactant were in widespread use. So you are not looking at a pure -- you have disease A, and it's either treatment X or Y. It's an amalgamation of treatments, and inhaled nitric oxide is being used in new application in those studies that you are seeing as is ECMO. Each physician is trying to assess risk and potential benefit, and use the therapies in additive fashion on the basis of at risk.

DR. PACKER: We will adjourn. After we return, I will ask Dr. Kinsella and Dr. Clark to return to the podium to continue the discussion on the indications for ECMO and the advantages and disadvantages of including ECMO as part of a composite endpoint.

We will take the break that was originally scheduled for us, which is 45 minutes and return here. We'll reconvene at 1:30 p.m.

[Whereupon, the meeting was recessed for lunch at 12:45 p.m., to reconvene at 1:30 p.m.]

A F T E R N O O N S E S S I O N (1:40 p.m.)

DR. PACKER: The first thing we want to talk about this afternoon is really to clarify and be able to have the committee address the issue of the advisability, advantages, disadvantages, of having ECMO as part of a combined end point in clinical trials.

This comes up frequently this afternoon. It is probably a good idea to talk about that before going into the results of individual studies.

In fact, before going into that, it would probably be a good idea to clarify from a clinical perspective what the indications for ECMO are.

The discussion was just beginning on that before lunch. Why don't we pick up at that point and I will just ask, how you know --

DR. CLARK: Let me show you two slides that I pulled out during lunch to help us with that. First of all, I think it is important that if we go back and ask the questions of patients who were referred to the ECMO center, that met ECMO criteria -- these are either by LDo or arterial oxygen differences or oxygenation index -- what percentage of those patients ultimately are treated with ECMO.

That number is a published number and covers

around 40 to 50 percent, depending on the patient mix. If we ask the registry question, what is reported to the registry as the reason for the initiation of ECMO into a particular patient, these have relative percentages between acutely deteriorated that is defined as a PA-2 less than 40 on rational medical therapy, and the feeling by the attending physician that the child is dying.

The oxygenation index better than 40, failure to respond to rational medical therapy, which depends on the specific therapy.

There is a small percentage where a variety of other things, progressive early, life threatening, hypotension, a variety of other reasons.

I don't think it is a simple statement to say precisely why specific patients have been put on ECMO. In general, the feeling is that the person taking care of the patient feels that they have met the criteria of more than an 80 percent chance that they are going to die.

How you define that is obviously a constantly-changing piece because of introduction of new therapies -- for example, high frequency ventilation -- so many of us have questioned the value of better than 40 in a patient who seems to be doing very well with high frequency ventilation. So, it is a complicated task to define.

DR. PACKER: Let me follow through on that. It

seems that the implications of what you have just said, by just pointing out the oxygenation index, there may be criteria that some physicians would use that others would not.

In order to make the ECMO criteria or use of criteria more persuasive, could protocols be designed so that ECMO would only be instituted under pre-defined clinical occurrences, as opposed to being left to the judgement of a physician or a investigator.

DR. CLARK: I think all the studies have attempted to do precisely what you are saying. The reality is that the attending physician, if it is in their best medical opinion that the child is dying, they are going to act in the best interests of that child.

So, if you ask me are the protocols precisely filed in each case, I would say that I don't know the answer to that, and I don't know of any studies that have looked carefully to say how often do people follow this protocol.

DR. PACKER: The way that sometimes we deal with that in cardiovascular trials is that we have a committee that, in a blinded fashion, reviews and adjudicates the use of an intervention to see if it met the criteria that has been defined as being associated with pretty generally accepted or formally accepted criteria. That would be the only utilization of ECMO that would count to the primary end

point.

DR. KINSELLA: When you have critical care decisions made at bedside at 2:00 o'clock in the morning, with somebody who has lots of multi-organ problems, and when you try to write those numbers down, there is always going to be an exception.

A lot of times these decisions are not necessarily being made by someone saying this patient has met an observation criterion for six hours, but there is something else going on.

At some point we make decisions. I find those things very difficult to define, write down on paper and have everybody follow.

We have to understand that we will make decisions as clinicians caring for critically ill newborns, and sometimes those decisions will be made the same and sometimes not.

DR. GOLDSMITH: I do not want you to confuse the ELSO registry, which is almost 14,000 babies now, the entry criteria for 111 centers with the entry criteria for the ECMO as an end point in the studies that we are going to hear about.

I think they are much more closely monitored and there could be a committee to look at the ones that didn't meet aligned criteria. I think that is possible.

I would like to take this opportunity to mention, for those of you who are adult physicians, that the demographics in pediatrics is also as different as the physiology that Dr. Moran mentioned so eloquently before lunch.

In this country, the United States, we deliver about four million babies a year at 6,000 hospitals, approximately.

About one in four hospitals has an NICU, which means they have a neonatologist. Less than 50 percent of those hospitals have pediatric cardiologists.

You wouldn't run an adult ICU without an adult cardiologist available to you to do ECHOs and things at the bedside. So, what we are talking about is that in 1,500 hospitals that have NICUs that might have the availability of treating pulmonary hypertension, 50 percent of them might do it without the diagnostic criteria being met, which is that the child has pulmonary hypertension by 2-D echocardiogram.

I think we have to be very careful in looking at the demographics of the treatment of children, neonates, in the United States versus what you are used to in terms of what you are used to in adult intensive care.

DR. PACKER: But the same situation occurs in adults. For example, in the area of heart failure, we would

like to think that all patients are managed as they would be at a specialty heart failure center. They would get an echocardiogram, et cetera.

We know that 80 percent of patients with heart in the United States are treated by generalists, and usually without any guidance or confirmation of the pathophysiology. So, it is not any difference in adults.

DR. GOLDSMITH: As you move toward a new therapy such as INO, and then recognizing that those 1,500 neonatal intensive care systems, only one out of 15 is going to have an ECMO, then you have to put the patient into a transport vehicle if he or she doesn't respond, and move them to an ECMO center.

So, we are looking at a degradation of the care available based on the centers, and I think we have to take that into account as we go forward.

In the centers that we are seeing, almost all of those centers that participated in these trials had ECMO available as rescue, and the children were immediately placed on ECMO, if they didn't respond. Forty percent didn't respond.

As we go forward, that would not be the case. If they don't respond, many of them are going to have to be --

DR. LIPICKY: You will see that one of the trials that will be discussed had rather rigorous criteria for what

they afford on the possibility of ECMO.

In fact, I believe it is something like the slide show just before. What was the number?

PARTICIPANT: Eighty percent of people approximately were transferred.

DR. LIPICKY: So, it was more than half?

PARTICIPANT: Yes.

DR. LIPICKY: Who were eligible received it.

PARTICIPANT: For the people that ultimately met ECMO criteria, the investigators were asked to check off what ECMO criteria they met. Of those, 80 percent of them the investigator said the criteria they met was an elevated oxygenation.

DR. LIPICKY: That is not the question. The question is, of those people who were eligible for ECMO by criteria, how many got it.

PARTICIPANT: Oh, a smaller fraction.

DR. LIPICKY: Something like 50 percent, which is roughly what you showed on your slide. So, when you do rigorously define criteria for ECMO, there are other things besides the numbers that you see that you can't define, that influence whether or not the ECMO is actually instituted.

That is why I was interested in understanding how the decision got made, and whether one could make a decision without some piece.

DR. CLARK: There is another complication of this, which is, if you look at most of these trials, the patient was meeting ECMO criteria at the time of enrollment.

Essentially, 100 percent of the patients -- probably not 100, but certainly close to probably 80 percent -- in both treatment groups, if I were to imagine based on the experience in other trials, would meet the ECMO criteria.

Something in the intervention changed the course of disease and allowed the patient to recover.

I think another important issue about this is to remember ECMO is not therapeutic. There is nothing in the ECMO circuit that reverses the underlying pathophysiology.

In fact, if you look at animal studies, ECMO hurts you. So, what is happening during the period of time that they are on ECMO is a spontaneous recovery, allowing things to rest and avoiding further injury.

I think if we do something else that promotes a similar type of recovery without causing any evidence of harm in a less invasive way, it is in the best interests of the patient.

DR. DAVIDSON: I would like to just address a question raised by one of the panel members about the correlation between oxygenation index and the need for -- neonatologists have generally used an oxygenation index of

25 to suggest that the baby may need ECMO, on the order of about 50 percent chance. That is from retrospective studies. When you hit an OI 40, there is about an 80 percent chance.

Keep your eye, now, on the trials that are coming up that are being presented, which are multicentered, randomized, blinded, placebo-controlled trials. You will see that the need for ECMO does correlate with the oxygenation index.

In the early treatment trial of Ohmeda, the oxygenation index was 25 on entry, and there was a 36 percent chance for those babies to go on to ECMO, pretty close to historical information.

In the INOS trial, where the oxygenation index at baseline was over 40, there was a much higher need for ECMO, in 60 to 70 percent.

DR. PACKER: I guess I don't really know what we would learn by thinking about what you just said. It is a little bit of a self-fulfilling property.

If the oxygenation index is used by many as an indication for ECMO, I assume there would be a correlation between the oxygenation index and the use of ECMO.

PARTICIPANT: I am from the University of Utah. I am a pediatric cardiologist. The question about, is there some way to make this a little bit more objective, my only

question is that neonatologists are very divergent in their use of ECMO. I don't know that it can be used with an end point.

I can tell by echo cardiology whether that patient has pulmonary hypertension at baseline. I can tell whether or not they regress because of pulmonary hypertension or some other mechanism.

There is some way to point, is this therapy preventing pulmonary hypertension.

DR. PACKER: Unfortunately, that doesn't quite solve our desire to make our decisions based on outcomes as opposed to physiology.

PARTICIPANT: Well, the choice is that death is going to be an end point. ECMO can't be an end point because, so you have to use oxygenation and pulmonary hypertension.

DR. KING: I think that we have an end point and the end point is patients with ECMO. It is very clear to most people in the audience.

You are describing a trial that can't be done and that is not really very helpful.

PARTICIPANT: I think you are describing a trial that can't be done.

DR. KING: What is your end point going to be. I think an end point of ECMO utilization makes a lot of sense.

It clearly will not get to survival.

PARTICIPANT: ECMO is used to treat pulmonary hypertension. You don't need to argue that at this point. You have to recognize what is going on. Tomorrow they are going to be making decisions about coronary artery disease where part of the end point is whether or not they need to be vascularized. Now, you tell me everybody makes the same judgement there.

It is clear that people's judgements to institute a procedure are different amongst individuals. The thing that I would like to see clarified is whether the decision to make ECMO is the equivalent of saying PA-02 is 14; therefore it is ECMO, but if it is 14.5 it is not.

The question you are leaving now is that that is the case. I don't believe that.

PARTICIPANT: With coronary artery disease, it is a little bit more simple. They just have coronary artery disease. [Laughter.]

DR. PACKER: Let me do the following. First of all, let me clarify that the purpose of today's meeting is really to explore the issues.

The position, I think, and charge to this committee is not to propose any specific finding. It is really to explore all of the advantages and disadvantages of all possible end points and their alternatives.

I don't think you have heard anybody on this committee say that mortality has to be the end point in trials. Nobody on this committee has said that.

What the committee has asked is that the C end point where death is combined with ECMO, we want to understand, one, why; two, what are the pitfalls of doing so; three, are there alternatives that no one has thought about and we might encourage.

So, we haven't designed any trials today. All we have done is explore the issues that could pertain to and be important to the design of future studies.

DR. LIPICKY: I would like to just offer my interpretation of the question that was answered, and it is clearly the answer that you have been getting from others, and at the moment I think what I am about to say is right.

Death and the initiation of ECMO, to me, are equivalent end points, with the exception that the initiation of ECMO accepts the notion that the person that is going to make the incision to place the catheters has decided that if I don't do this, this patient is dead.

In that sense, it is a true surrogate for mortality. It is for sure that the decision making process, for whether or not to do ECMO varies from individual to individual.

Although nobody has said it, I have had people

tell me that they would have instituted ECMO with PO2s that were perfectly okay, because other things were going bad.

No one would entertain using oxygen if they didn't think oxygenation was a problem. Clearly, you have to believe the baby has an oxygen problem or you wouldn't entertain doing that.

There is much more to the decision-making process, it seems to me, than simply the PO2 isn't somewhere. I don't know want to go in and say what that decision-making process entails.

DR. PACKER: Maybe we could try to clarify things along the following lines, and then take some more comments. I guess there are two ways -- three ways -- to think of ECMO that would support issues as a part of the composite.

First, Ray, as you have just outlined, it is equivalent to death in an ethical world. The baby's physician has made the judgement that, unless the baby gets ECMO, the baby is dead. That is one possible way of thinking about it that would support its use as part of the combined surrogate.

The second is to say that it is not a surrogate for mortality. It is a reflection of a deterioration in clinical status which itself is clinically relevant.

In other words, to be clinically relevant, death is not the only clinically relevant event that can happen to

a baby.

Therefore, ECMO is simply the physician's way of signalling to someone that the baby has done so bad and has met certain clinical deterioration criteria that that, in and of itself, represents a real clinical event, and not a surrogate for anything.

The third way of supporting the use of ECMO as part of a combined end point is to consider the quality of life issue, or an avoidance of risk issue, or a reduction in cost issue.

I am lumping these all together, although they are not all related to each other, but focusing on the quality of life issue.

It is unpleasant. It then carries risk to be on ECMO versus not being on ECMO. This is analogous to the discussion that took place earlier this morning, on whether it is better to not be on the ventilator than to be on the ventilator.

I have concerns about that argument because the institution of ECMO in these trials is not really analogous with the weaning of someone from a mechanical ventilator.

The difference is, in all the trials of ARDS, the patients were on the ventilator a priori, before the trials began, and the idea was to make them better.

Therefore, the weaning of the patient from the

ventilator was a quality of life issue. Here, the babies are not on ECMO at the beginning of the trial.

Consequently, it is the physician who is making the judgement to impair quality of life as opposed as there is an impairment in the quality of life with the potential to get better.

That is being done for a good purpose, i.e., life saving purpose. Therefore, I guess I am reluctant to get into the third category, because I think that is very different than the ventilator example.

I personally think that the solution that I would favor would be to think of it in the second category. That is, this is not a surrogate. This is not a quality of life issue. It is a reflection of clinical failure.

What I would like to hear is what the committee thinks about any of these possibilities or others or potentially rejects them all.

MR. CALIFF: I would like to speak in favor of both two and three. I actually think Ray has a good case on item number one, too.

It is apparent, if the child has been in a neonatal intensive care units, having a child with these tubes coming out, and the potential sequelae of that, I think, is a horrible thing.

I don't know of any physician who would institute

ECMO for the fun of it. It really is an indication -- it is such a horrible thing, no parent would stand for it, unless there was a real belief that unless you did it, the outcome would be terrible.

I like your argument number two, that it is a clinical failure. I also think that, at least as the best estimate you can make for a little baby, it can't be a good thing to be lying there with cannulas in your back for a few days.

I think there should be at least some credit for item number three.

DR. PACKER: I guess the reason for my skepticism about item three is that if one takes that rationale and extrapolates it to areas other than the one that we are talking about today, you get into problems.

For example, if you were to say, PTCA, per se -- we were talking about coronary disease before -- is a procedure that impairs quality of life.

So, if you had a drug that reduces the use of PTCA, without reducing the clinical indications for which PTCA is indicated, you get big problems.

That would strongly favor two and lead you to be much less enthusiastic about three.

DR. CALIFF: I think your point is well taken, that it is a classic fact that this point number three

should not be generically extrapolated.

I would put this in an extreme category of therapies. In a lot of centers having a groin is an indication for PTCA. But I think that ECMO is probably a very different category of therapy.

I think argument number two is so strong that you don't necessarily need argument three. I just think there should be a little credit given.

DR. GOLDSMITH: I would echo what Dr. Clark had said before, which is that there is no therapy that ECMO provides. It provides lung rest.

If we think that we intercede instead of ECMO, such as the therapies that Dr. Walsh-Suchy has talked about, giving four or five therapies before you come to ECMO and now adding INO on top of that, would mean that the baby is being continued on a ventilator at potentially toxic settings.

One of the reasons we used ECMO before OI criteria are met, is because we think that is on toxic settings that will lead to chronic lung injury.

If we delay -- there is at least one, maybe two studies that show this now -- if we delay ECMO initiation to allow the patient to stay on the ventilator at toxic settings, we see an increase in bronchopulmonary dysplasia chronic lung diseases.

So, one of the outcome measures -- and I agree with the three that you have given -- but one of the measures that needs to be looked at for using INO before ECMO initiation is the increase in chronic lung disease.

DR. KONSTAM: I wanted to comment on your thoughts. I could personally accept any of the three constructs, and I am most attracted to the second one, as you are.

That is to say, that this sounds to me that this is a very concrete marker of badness in the child, of a judgement on the part of the person in the trenches caring for that infant, that that infant is very critically ill.

Now, we have been struggling to identify the objective criteria that have pushed that, but that is okay. What that means is that there is not a one-to-one relationship between oxygenation, which is okay, because if there were a one-to-one, then we would just look at oxygenation.

So, it is something more than that, and I guess that I also would -- it is appealing to try to identify all the objective criteria that uniformly result in a decision, but you know you will never succeed at that.

Based on what you are hearing, it sounds pretty convincing that ECMO in its day has significantly reduced mortality.

Therefore, we can go through this step of reducing the number of times that the clinician thinks that the child is sick enough to require ECMO and, at the same time, convince ourselves that we are not doing that by having a greater mortality.

Then I think it is appealing that we have, in fact, done something to alter the disease, or at least the perception of how sick the kid is.

DR. LIPICKY: There is a reason, I guess, to go through the relative -- I don't want to end the discussion of trying to say whether this is surrogate death or it is something else or it is something else, because there is value to that.

One of the values to that is, again, coming back to urgent interventions, our agenda has been set to progress with this question tomorrow as if a trial on coronary artery disease is primarily settled on the basis of urgent interventions.

Even if it is a fairly spectacular trial, go back and do another one to convince us, because that is not irreversible end points, and we are not comfortable with making decisions on the basis of non-irreversible end points.

So, in part, the decision about where ECMO sits, whether it is a surrogate for mortality or some less

meaningful irreversible indicator, in part it raises the standard.

DR. PACKER: I think that is why the discussion about which of these three criteria, or perhaps other possibilities, is so important, because if we can define what our thinking is in this area, we can perhaps establish a sense or even a guidance for future clinical trials that would use ECMO as part of a composite end point.

We need to always sort of at least look on both sides and realize that whatever decision we make has to be consistent across therapeutic categories.

It would be a little bit silly for us to criticize the inclusion of revascularization or any other procedure in a combined end point, but raise ECMO simply for quality of life or economic reasons.

DR. TEMPLE: There probably has to be some logical consistency across therapeutic classes. That doesn't mean you necessarily reach the same conclusion on each of them, because each one of them is going to be a different situation.

I just want to follow up on the logic of the first category. If I understand you, just saying that this represents therapeutic failure is one step short of getting there.

I think it is crucial that you also believe there

is evidence that the intervention that you are preventing, because someone calls it therapeutic failure, actually preserves life, and there is some evidence of that.

That means that you are preventing something that is therapeutic failure that really would have led to death. You have just prevented it, and you actually have methods for doing that, and that seems a component of this.

That might make this different from other kinds of interventions, for example.

DR. PACKER: Bob, let me take what you just said and put it into an analogous situation closer to some of the diseases we think about.

In the area of heart failure, there are two kinds of interventions which have been used combined with something as a primary end point, two extremes.

First is transplantation. The second is increasing background medications. Both of them can be used to designate a treatment failure, but we are, I think, understandably reluctant to think that an increase in background medications is good enough to be included in the composite, but we routinely see clinical trials that assign to transplant a status equivalent to being dead.

That is not necessarily always true but I am trying to provide an example that is analogous to your example. Do you agree with that?

DR. TEMPLE: I think the increase in medication has some different function. I think it really represents an attempt to, in a sort of combined or global way, measure the degree of failure that the person had.

If someone told you that you could intervene and decrease the amount of failure the person has over time you would say, that is good. This is just the way we measure it and it is easier to count than other things.

So, that strikes me as a measure of progress of the underlying disease. Most of the time you would say preventing the progress of the underlying disease is good.

Using intervention in a coronary artery setting is probably more debatable, but there are certain bad things -- trust me on this -- associated with having PTCA.

Preventing that in a benign way that doesn't take anything else away seems to be a pretty good benefit. Ray wasn't denying that. He was just saying we would probably like to see that demonstrated more than once because it is not as obvious and urgent a result.

DR. PACKER: Bob, I don't understand, and maybe Ray can clarify. If you demonstrate something you don't believe in twice, do you believe in it more?

DR. LIPICKY: It is the ethics of asking for it a second time. If you have a pretty strong, irreversible end point trial, you have to wonder whether you can ask for it

again.

So, you would say, okay, I don't really believe in it but I can't ethically walk the streets and ask for another one.

If you don't have irreversible time, then you can say, I don't believe it.

DR. TEMPLE: It is not really not believing in it. It is how sure you are.

DR. PACKER: Wait a minute. I guess what I think I hear you saying is that you actually think that the avoidance of revascularization is reasonable. You just want to see it twice. Because it is reversible, you can ask for it twice.

DR. LIPICKY: That is not quite right, but it is close enough that I will accept it.

DR. TEMPLE: There are two different subjects here. One is level of evidence that you need to believe something or prove something. The other is what is a valid end point.

Nobody is expressing a doubt that preventing revascularization is a valid end point.

DR. LIPICKY: Yes, it is a valid end point. No problem with that.

DR. THADANI: I think before we go on to discussion, the data here on the British study was thought

premature. You are accepting that ECMO is preserving life. The panelists are not contesting that statement; is that true?

From the data that we are being given, including the British study which is the one that you showed, compared to conventional treatment and revascularization, that ECMO improves the life.

If that is true, then how can we suggest that you can offer an alternative treatment if that was available, that you are going to withhold that treatment.

In order for me to accept something else, you have to show that ECMO or some other treatment is either reducing the hospital stay or reducing hyperventilation. I haven't seen anything like that. Would that be the kind of thing that we would like to see.

How can you deny, if ECMO is available, and your child is dying, that you are going to keep on trying until he is nearly dead. The question comes up how many children are dying because you are not giving them ECMO and they don't go into the trial results.

DR. CLARK: Let me try to approach that, just briefly. I think what you are going to see next is to try to get at that issue, precisely. I think that the question that will be before us is not whether we avoided ECMO.

The question you asked is much more important, and

that is, did we do that in a safe manner. In other words, is the outcome of the patient who is treated with nitric oxide equivalent of that that was in the control and not on nitric oxide.

That is, as I suggested in the last slide, a very difficult issue to get at with regard to numbers, because it comes to the whole issue of what is equivalent. How much are we willing to accept, as was addressed this morning, in differences. How certain can we be that things going the wrong direction in many of these studies are not really events.

My argument to that would be that part of what we need to do is in communities -- and we have actually set this up -- is to collect a larger data base of information on these patients as we go forward, to look and see if there are any other adverse events that are occurring at a very low rate that we are not measuring in the current trials.

DR. THADANI: I think the issue also comes up to me and which I am thinking might be a tentative for ECMO is one to zero. So, you have to randomize one to ECMO and one to the conventional and one to something else.

I think I would like to see them work out the effects of the holding therapy in that time period. I would like to know a little more on that.

DR. ALTON: I have applied both techniques to

neonates, pediatric patients and adults, ECMO and nitric oxide.

I think one of the concerns for me, in listening to the committee, seems to me to be some of the misunderstanding between what are some of the desires we have as clinicians.

It is proved that ECMO saves lives in neonatal patients and it probably saves lives in selected pediatric and adult patients as well.

However, on the continuum of therapies that you would like to use versus never use, ECMO is on the never use end. It is very invasive; it is very costly; it is very labor intensive.

While you don't necessarily want to deal with those issues in focusing more on quality of life, it is very important to remember that you are doing ECMO, and it is very expensive, it is very labor intensive, it takes a lot of manpower.

The complications, when they do occur, are very severe -- bleeding in the head, et cetera, et cetera. To find something before you get there, that works equivalently well, would be terrific. We would love it.

I can tell you that in pediatric patients who come to my center for pediatric ECMO, of which I believe the oxygenation index is a good screen for how sick they are, if

they have responded to nitric oxide, they may improve their oxygenation and I am able to reduce the amount of pressure I am beating them with the ventilator and the amount of oxygen that I am giving them.

Their survival has been equivalent to those patients who I would have put on ECMO for similar criteria in years past.

In patients who don't respond to nitric oxide, however -- these are older patients -- their mortality even with ECMO has been poor, which is a lot different than in the neonatal battery.

I think in the neonatal battery that is available now, either in printed form, in published form, if you look at patients who have either gotten nitric oxide, high frequently ventilator, et cetera, et cetera, before they go on ECMO, there has not been a great change in mortality based on previous therapies.

That indicates that all these therapies -- that is what is nice about them; you can give surfactant; you can give nitric oxide.

We know if it works within a fairly short period of time and you can move from them onto the more invasive things.

I think it is a misunderstanding of the committee that we would like to do ECMO on everybody. That is not

true. I think the goal of ECMO would be to find something that would make us never have to do it again.

I think it is reasonable to look at ECMO as an end point of therapy. I kind of agree with Dr. Lipicky's comment, that in patients that you place on ECMO, we do believe they are going to die. It is certainly okay to lump that as the surrogate.

I really think that the idea that we want to use ECMO as equivocally as nitric oxide is probably not true. We would like to use nitric oxide to replace the need for ECMO.

DR. PACKER: I don't think anyone on the committee thinks that anyone uses ECMO or institutes ECMO lightly. I guess it would be important because this has been, I guess, a recurrent theme all through the day's hearing, that there may be many of you in the audience who may be puzzled by the kinds of questions we are asking and why it would appear that we are making this process so complicated.

Shouldn't this be simple? You know, you just measure the PO2 and if it goes up, clearly there is clinical benefit. Why are we making this so complicated.

We realize that everyone on this panel is someone who takes care of patients. We do understand your position.

The problem is that the regulatory decision making process is a very different process from the clinical

decision making process.

That is because we have heard a lot about the analysis of clinical trials which can be misleading and which can result in therapies that are not as good as physicians think they are.

So, it is very important for us to define what we are looking at to define the criteria in which judgement will be based, and to do that in a fair and balanced fashion.

That is not identical to the process that physicians follow when they are taking care of patients. It is important to understand that distinction.

DR. KINSELLA: It is also important to understand that you can think over the issues of how ECMO is applied, but the reality is that it is used as a standard treatment when all else has failed in newborn intensive care units around the country.

There will not be a randomized trial using ECMO alone. That is done and people are sold on it. I think that is correct.

So, what we have to say, to us that is the last step. How are we going to design studies to design new therapies? I think that is the right thing to do.

DR. PACKER: Just understand that it is important for us and for the agency to understand why you feel that

way, and to understand whether the reasons you feel that way, if it were applied to this area or other therapeutic areas, would get us into trouble.

What you are convincing us of, and I think you are hearing that, is that we are persuaded that the way you are thinking about this is not likely to get us into trouble, is not likely to get us into trouble.

What I am trying to say is that you are convincing us. What we need to work through is the process of understanding why avoidance of trouble is likely.

DR. ROTHSTEIN: I thought I heard a couple of minutes ago members of the panel concerned about withholding ECMO, because it might be life saving, and trying a new therapy.

There is a simple mechanistic answer to that. In the time that it takes to mobilize a surgical team and start the process of getting the cannulas implemented, I can slap nitric oxide into a circuit and have a 30-minute trial and know whether or not I have a responder or non-responder.

I can accomplish both, offer both, but also having that trial of seeing if the child is responsive to nitric oxide.

If it is not responsive, you can proceed with ECMO. If it is responsive, the child may no longer meet the ECMO criteria.

DR. KINSELLA: Or you may make that cannulation procedure considerably more safe by stabilizing the patient.

DR. PACKER: Please understand that the reasons these discussions are taking place is that it would be a real crime if nitric oxide was used and we convinced physicians not to implement ECMO, delay it, and it was wrong.

If nitric oxide didn't work, if you could not persuade yourself that it worked, then in fact, the utilization of nitric oxide to increase PO2, unless that was shown to be clinically relevant, would result in horrible judgement in terms of the delay of life-saving interventions.

DR. ROTHSTEIN: But many of the diseases we are talking about here, a rise in PO2 is directly related to the underlying pathophysiology.

We are not talking about pseudomonosepsis that is destroying the heart, the kidneys, the lung. We are talking about an abnormal tone of the pulmonary vasculature. The rise in PO2 is giving me evidence that, in fact, I am getting at the basic problem.

DR. PACKER: The fact is that I haven't heard anyone say that that rise in PO2 is the primary end point of the problem.

Everyone is saying that the primary end point is

death or ECMO. That is what we are hearing. No one has proposed that the change in PO2 be the primary end point.

PARTICIPANT: Can I just suggest that a lot of the data that will be presented in the next studies will present this precisely.

DR. PACKER: Could I ask those at the microphone, just for the sake of time, please come back in about a half an hour. We will proceed with the discussion of the clinical trials.

Agenda Item: Clinical Trials. NINOS.

DR. EHRENKRANZ: Good afternoon. I am Richard Ehrenkranz. I am clinical director of the newborn Intensive Care Unit at Children's Hospital at Yale.

The neonatal inhaled nitric oxide study was a multi-center trial performed by eight members of the NICHT, neonatal research networks, in collaboration with the 10 members of the Canadian inhaled nitric oxide study group.

It was a randomized, controlled, double masked clinical trial, in which infants were randomly assigned to an inhaled nitric oxide treatment group or to a control group.

The primary hypothesis stated that treatment with inhaled nitric oxide reduces death and/or receipt of ECMO from 50 percent in the control group to 30 percent in the inhaled nitric oxide group, a relative reduction of 40

percent.

A sample size of 250 patients, 125 patients per group, was estimated to be necessary to demonstrate this reduction at a P level of .05 with 90 percent power.

The secondary hypotheses for this study were that treatment with inhaled nitric oxide would lead to an increase in PA02 and a decrease in OI and PO2 measured 30 minutes after the initial administration of study gas, a decrease in the length of hospital stay, no change in the duration of the cystic ventilation and the incidence of pulmonary air links and bronchopulmonary dysplasia, bronchopulmonary dysplasia being defined as oxygen dependence at 28 days of age with an abnormal chest X-ray.

Further, there would no change in neural development or disability at 24 months follow up date.

The inclusion criteria for the study are listed on the slide. One. Infants need to require assisted ventilation for hypoxic respiratory failure that resulted from a diagnosis of persistent pulmonary hypertension, respiratory distress syndrome, meconium aspiration pneumonia, pneumonia sepsis, or suspected pulmonary hyperplasia.

Infants with congenital diaphragmatic hernia were enrolled in a parallel pilot trial that followed the same outline as the trial that I have described to you.

OI was greater than 25, greater than or equal to 25, in two arterial blood gases that were more than 15 minutes apart, an echocardiographic evaluation within 24 hours preceding randomization, and an ingoing arterial line, and consent by the parent or the legal guardian.

The exclusion criteria for this trial were distinctional age from greater than 24 weeks, a gestational age of 34 weeks and a postnatal age of greater than 14 days, congenital heart disease, other than arteriosus or mitrial level shunt, and a decision not to provide full treatment -- for example, secondary seizures, multiple brain injury.

Inhaled nitric oxide was considered an investigational therapy. Therefore, all conventional means of treating infants who were potential candidates for the trial were to be employed before randomization.

The study protocol did not specify details of pre-enrollment management. However, each participating center developed general management guidelines that were used for the duration of the study and agreed to institute maximal conventional therapies before randomization.

We believe that this strategy is one of the strengths of this trial. I show on this slide the general management guidelines, including the maintenance of a mean blood pressure greater than 45 millimeters of mercury, induction of alkalosis with a target pH of 7.5 to 7.60,

provision of sedation and neuromuscular blockade, surfactant therapy.

Surfactant therapy could only be administered after randomization if it had been given prior to the initiation of the study drug. Finally, high frequency ventilation.

The load of ventilation could not be changed once the baby was randomized into the study except as part of weaning.

Therefore, the infant was randomized on conventional ventilation, if they were staying on ventilation throughout the study. However, if they were randomized on high frequency, they would remain on high frequency in the study, and removed from high frequency as appropriate and then placed on conventional ventilation.

It was expected that infants would be randomized as soon as possible after meeting eligibility criteria and obtaining the second OI greater than or equal to 25.

Infants were randomized to INO or control. They were randomized by an automated telephone randomization system and they were stratified by center.

Infants were evaluated at 20 parts per million nitric oxide or controls at 100 percent oxygen for 30 minutes.

At that point, arterial blood gas was obtained.

If the PA increase was greater than 24, they will continue at that level of study gas, 20 parts per million of nitric oxide or control.

If the PA02 is less than or equal to 24, they were evaluated again after treatment at a level of 80 parts per million. If the PAO2 increased at 80 parts per million, or had obtained 24, they were treated at the lowest dose at which they responded.

Specifically, if the PA02 increase was between 10 and 24 at both the lower and higher levels of study gas, the infant would receive the lower level of study gas.

However, if the PAO2 increase was only obtained at the higher level, the infant would remain at the higher level of study gas.

Finally, if the PAO2 increase was less than 10, the study gas was stopped.

We permitted two-week trials of study gas. Each treatment had to be at a six-hour interval and only if the infant was still eligible. Cross over was not allowed between study groups.

Study gas management was performed by designated unmasked individuals. Algorithms for study gas weaning, escalation and reinitiation were suggested by the protocol.

There was a 14 day cumulative maximum of study gas treatment, 336 cumulative hours.

Finally, the decisions to initiative ECMO were made by the clinical team using center-specific criteria.

Blood and methemoglobin levels and the concentration of arterial nitric oxide and nitrogen dioxide were monitored by unmasked individuals. These included our research nurses and respiratory therapists.

If the methemoglobin level rose to between five and 10 percent, study gas was weaned until the methemoglobin level was less five percent. If the methemoglobin level increased over 10 percent, the study gas was to be discontinued.

If the nitrogen dioxide level increased to between five and seven parts per million, study gas was to be weaned until the O2 level was less than five parts per million.

If the NO2 level increased over seven parts per million, the study gas was to be discontinued.

In addition, we had a number of study site certification procedures. Study sites were visited by a certifying team that consisted of the principal investigator, an experienced research nurse, coordinator, and a senior member of the biostatistical center.

Quality assurance procedures were reviewed at that time. Masking procedures were also reviewed. Masking procedures needed to include how the flow meters would be masked, INO and NO2 readings, the methemoglobin levels,

whenever we got them back from the laboratory, could only be reported to unmasked individuals, mock adjustments of the flow meters, and mock changes in tanks, or changes in tanks, depending upon what was happening.

A written certification exam was also completed by the co-investigator, the research nurses and the respiratory therapists involved in this trial.

This is an example of the ecophysics hemiluminescence analyzer that was used. This is the one at Stanford. This was before masking, an example of how the readouts of the flow meters are masked; a little bit closer.

This is Indiana University, a similar masking of the readouts on the flow meters. Similar procedures were evaluated at every procedure to ensure that appropriate masking procedures were in place, and that the unmasked individuals had put in place appropriate monitoring of the methemoglobin and NO2 levels.

As you are aware, this trial was terminated at the recommendation of an external data safety and monitoring committee, after the second planned review of the data showed that the Z value had crossed the prevalued boundaries of statistical significance.

After that recommendation was reviewed and accepted, patient recruitment ceased on May 2, 1996. At that time, 235 patients, as opposed to the 250 initially

felt necessary, had been enrolled, 121 in the control group and 114 in the INO group.

As shown on this slide, there was no difference between the birth weight, gestational age, percent males, percent white or percent outborn, between the study groups.

Of the outborn infants, about 50 percent of them were transported and had been admitted to the receiving center by 12 hours of age, approximately 12 percent between 12 and 24 hours of age, and about 30 percent at greater than 24 hours of age.

The diagnostic categories with respect to the type of lung disease causing the babies to be transferred, you had the pulmonary hypertension of the newborns, respiratory distress syndrome, meconium aspiration syndrome, pneumonosepsis, and other suspected pulmonary hyperplasia, were no different between the two treated groups.

With respect to treatment modalities before randomization, remember, we did not specify in the protocol how the infants were to be treated.

We wanted them to receive what was considered the maximum conventional therapy at the institution before randomization.

As you can see, there is no difference between the frequency that volume support or vasosuppressor support was utilized between the group, Tolazanine, one of the non-

specific drugs that was used in the past for pulmonary vasopulmonation, sedation, analgesia, neuromuscular blockade, induction of alkalosis, surfactant -- a little over 70 percent of the infants received surfactant prior to the therapy, and 55 percent had been exposed to high frequency ventilation prior to randomization.

Thirty-seven percent of the control, and 32 percent of the inhaled nitric oxide infants were on high frequency ventilation at the time of randomization.

At the time of randomization -- this is data from the first qualifying arterial blood gas. Remember, we said that babies would be eligible when their blood gas was greater than or equal to 25 on two arterial blood gases at least 15 minutes apart. This is data from the first gas.

The OIs averaged just about 45 in both groups. The average age at the time of randomization was 1.7 days, which is roughly 41 hours.

The median time from randomization to study gas onset was 10 minutes in the control group and 15 minutes in the INO group.

As previously stated, an OI of greater than 40 is the most common reason that infants are placed on ECMO. Therefore, since many infants already met ECMO criteria, at the time of randomization, we would not expect to see any difference in the number of infants meeting ECMO criteria.

In fact, because of concern raised about them, we have actually gone back and started pulling charts of infants.

We have found that approximately 58 percent of infants actually met ECMO criteria at the time that they were randomized.

The other thing that I want to point out is that in our study design, we hoped to randomize infants with OIs greater or equal to 25. Therefore, these infants were much sicker at the time of randomization than we had anticipated that they would be.

This is the response data to the initial administration of study gas. This would be 20 parts per million of nitric oxide or control.

For increases of less than 10 torr, that is legally defined as no response. Partial response is if PO2 increased from 10 to 20 torr, and a full or complete response if PO2 increased to greater than 24.

By our definition, infants who had this response would be remaining on the study gas at that level. Infants with these responses would be exposed to the higher level of study gas.

Significantly more nitric oxide treated infants than controlled infants had at least a partial response to the initial study gas administration, 66.1 percent versus

25.6 percent.

Furthermore, of the infants who did not have a full response at the lower level -- 20 parts per million nitric oxide or control gas -- and who were evaluated at the higher, 80 parts per million nitric oxide or control -- 77 percent of the NO treated infants and 84 percent of the controls had no response to the higher study gas concentration.

Data here is only showing 229 infants. As I noted here, four control infants and one INO treated infant did not receive study gas and the data are not available. These data are analyzed by the treatment assignments and the intent-to-treat analysis.

These are the physiologic responses. These are really the secondary analyses of these data. These are measures of oxygenation, and the data demonstrate that inhaled nitric oxide produces significant improvements in oxygenation.

We see that as changes in PAO2, in control just shy of 10, to our inhaled nitric oxide group of 58. There was a change in OI with no change in the control group, a decrease of -15 in the INO group, and a change in PAO2, change of just about 7 versus 60 with the INO group. Each is a highly significant difference.

With respect to our primary outcome, we used a

primary outcome as death and/or ECMO. You can see that by the intent-to-treat analysis of the 121 infants in the control group and the 114 in the INO group, our primary outcome is highly significance, the difference 63.5 percent of the infants in the control group had a primary outcome versus only 45.6 percent in our INO group.

There was no difference in the incidence of death between the groups, with the real difference being in the incidence or the number of infants that received ECMO, 54.5 percent of the control infants versus 38.5 percent of the INO treated infants.

As I just mentioned, data were analyzed in the treatment group into which they were randomized; that is, they only had intent-to-treat analysis.

Furthermore, there were seven infants who were identified as having received the wrong study gas were analyzed according to the treatment actually received.

In conclusion, we feel that nitric oxide significantly reduced the primary outcome -- death or the use of ECMO -- in infants with hypoxic respiratory failure, in general. So, there is a significant benefit of inhaled nitric oxide.

In an effort to further address concerns about whether the treatment method was maintained, we have also determined the percentage of infants who did not have a PO2

increase greater than 24 in response to the initial administration of study gas, and who were treated by ECMO.

As seen on this slide, 15 percent of those infants who were non-responders in the control group, 58 percent of those infants who were non-responders in the INO group went on to require ECMO.

However, only 23 percent of the responders in the INO group required ECMO, compared to 47 percent of those responders in the control group.

We believe that this analysis demonstrates that issues other than short-term response to the initial study gas administration were involved in the decision to initiate ECMO, and that those issues were considered without bias to both study units.

The data I have shown on this slide show treatment modalities used after randomization: surfactant, high frequency ventilation and steroids.

As shown here, there was no significant difference between any of these post-randomization therapies. Again, we feel that this is consistent with our belief that there was no evidence of any systematic bias in the performance of this trial and that all infants enrolled in this trial were treated similarly after randomization.

This slide looks a little bit more closely at the deaths. There were 20 in the control group, 16 in the INO

group. Nine control infants and eight infants in the INO group received ECMO.

Of the other 19 deaths who did not receive ECMO, there were contraindications of ECMO present in 10 infants -- five in each group. Life support was withdrawn in five infants in the control and two in the INO group.

Center-specific ECMO criteria were not met in three controls and one INO group.

With respect to some of the short-term outcomes in surviving infants, there is no difference in the number of days of hospitalization, days of assisted ventilation, the number of air leaks after randomization or the development of bronchopulmonary dysplasia.

In addition, with respect to adverse events after randomization, you have seen this slide earlier in one of the other presentations.

The infants are monitored for intracranial hemorrhage, specifically grade four, periventricular leukomalasia, brain infarction, seizures requiring treatment, pulmonary hemorrhage and GI hemorrhage. Again, there was no difference in any of these adverse outcomes.

No infant had study gas discontinued for toxicity. We treated infants with 2.4 plus or minus 1.8 percent, and the mean peak NO2 level was 0.8 plus or minus 1.2 parts pre million.

INO was lowered in 11 infants due to elevated methemoglobin levels. In the study design, if the level was between 5 and 3 percent, the nitric oxide or the study gas had to be lowered. It was cut in half and the values repeated to bring it down to less than five percent.

So, the INO was not lowered in any infant due to elevated nitrogen dioxide level.

As part of our study, we included long-term follow up at 18 to 24 months of age in these infants. This follow up is still going on. This is preliminary data for 75 control infants and 79 nitric oxide infants.

The number pending, there would be a total of 101 in the control group and 98 in the nitric oxide group.

The evaluators for the developmental follow up were masked as to whether the infants received nitric oxide or control treatment.

The chronological age at the time of follow up is 20.9 months versus 20.3 months. Severe mental delay is defined as a mental development index of less than 50 -- three versus six.

Severe cerebral palsy, this is based on the number of infants who could be successfully treated and tested; no difference.

Infants with sensory neurohearing loss, 11 and 12. Seizures after discharge, nine versus four. Need for

assisted ambulation, three and six; no significant difference.

This is the preliminary data of the number of infants who required hospitalization after discharge; no difference.

The causes for hospitalization; respiratory causes was the most common cause. CNS causes, just about 10 percent.

A similar number of infants were discharged on oxygen from both the treated and the control group. The duration of oxygen at home was similar. The use of bronchodilaters after discharge was similar. There were no late deaths in the control group and one in the INO group. I do not have the cause of that death.

In conclusion, inhaled nitric oxide reduces the use of ECMO in critically ill neonates with hypoxic respiratory failure.

INO appears to be safe, well tolerated, and without short-term toxicity. INO does not appear to result in increased development of disability in infants at 24 months chronologic age.

INO does not appear to result in an increase in long-term respiratory sequelae. Thank you.

[Applause.]

DR. PACKER: Due to difficulties of bringing

everyone back up, I think we should probably take a question or two after each presentation.

DR. KONSTAM: I would like to review this issue of the infants who received the wrong study gas. I am confused on a number of different points on this. One is exactly the numbers that are involved.

In the reviewer's write up, it says that there were seven infants randomized to control who actually received nitric oxide; is that right? I didn't notice that you said it that way.

DR. EHRENKRANZ: I said after the primary -- this data is based on 229 infants. This is intent-to-treat analysis as shown on this slide. Physiologic data, same data, intent-to-treat analysis.

This here is the core study group. This includes intent-to-treat analysis with the infants who received the wrong study gas.

There were seven infants who received -- control infants who received nitric oxide. There was one study infant who received control treatment, who was supposed to receive nitric oxide. We did the same analysis.

DR. KONSTAM: The analysis is part of my concern. So, we do have the numbers right. So, in other words, seven infants who were randomized to control received nitric oxide instead. There was one child who went the other way.

In the FDA review it says, six of the seven subjects who incorrectly received inhaled nitric oxide ultimately received ECMO and two of the seven died.

This concerns me on a couple of different grounds. One starts to begin to question which is the best analysis now, because one point is that so many of these incorrectly administered patients, in fact, reached end point.

So, you start to really question what should be believed. Should we believe the intent-to-treat analysis or should we not.

I know it still reaches statistical significance in both, but the significance of the primary end point declines if you look at it in terms of the kids that actually got the particular drug.

DR. EHRENKRANZ: For those who received ECMO, here it is .017.

DR. KONSTAM: Right, but this is the ones who actually received the drug.

DR. EHRENKRANZ: This is the intent to treat. If you look at it the other way, this number is .017.

DR. KONSTAM: That is not actually my biggest concern. Let me just finish. That is not actually my biggest concern about it.

My biggest concern about it is why this happened and why were there seven kids who got the wrong treatment,

and why is it that six out of these seven kids had to get ECMO.

What it raises is a concern in my mind as to the integrity of the blindedness within the trial. Maybe we need to talk about this a little bit more, because it sounds as though there were unblinded investigators at every sight.

We know that there are other ways of effectively being unblinded because you see what happens in the PO2.

I think this issue is worth dwelling on when the principal end point is a suggested end point, and it is being driven by the judgement of the investigator.

Now, I think that is really where I am heading here. In order to really have faith in the subjective end point, you would like very, very much to have retained the integrity of the blindedness.

I am concerned that this observation of these seven kids who were put on nitric oxide is, in fact, a signal that there was a significant problem with the integrity of the blindedness during the trial.

DR. EHRENKRANZ: The people who had control over the nitric oxide, who had control over administering it, were unblinded individuals. They were respiratory therapists or research staff.

They were not involved in the clinical care of the baby and they were not involved in decisions of who was

placed on ECMO and who was not.

They had guidelines and procedures in which they had to report different information and were protective of that information.

DR. KONSTAM: Could you just comment on how you think it happened that seven children randomized to control actually got nitric oxide, and what it means that six out of those seven ultimately went on ECMO.

DR. EHRENKRANZ: I think it means that not every baby responds to nitric oxide, number one. Joe, if you can shed some light on this, because I can't.

Joe Hedder was the lead statistician for this project.

MR. HEDDER: There actually were reasonable reasons. We were actually doing two trials at the center, one in CVH babies and one in non-CVH babies.

The CVH babies were randomized under coding A. Non-CVH babies were randomized under the B code.

One baby was inadvertently randomized because the coordinator thought A was active and B was control. There are other instances that reflected -- I have a list here and I could present them later.

In most cases, they were errors done in the masking by the clinical people.

DR. KONSTAM: But it wasn't a symmetrical error.

Seven of the eight mistakes were in the direction of the kids who were randomized to control getting nitric oxide.

MR. HEDDER: That is correct.

DR. KONSTAM: It is a high number to begin with. It just seems odd.

MR. HEDDER: Actually, I think in most trials there are errors. If you want to call it high, I don't think I want to get into the argument.

Certainly, the FDA received the data that indicated why these individuals were treated in that fashion. Admittedly, I was part of the study, I have a bias, but I don't think it was because of the bias that they were unmasked. They were just errors.

DR. CALIFF: Actually, this is just a comment on Marv's comment. The asymmetry, I think, is of a little concern.

The frequency in a trial where you have got incredibly ill patients and you are trying to do things in a hurry, this is not an uncommon number of times to have foul-ups.

It is the asymmetry that is a major issue that maybe can be explored more.

I have a question that, although the differences in the use of high frequency ventilation and surfactant were not significant, they were trending in the wrong direction.

I wondered if adjusted analysis for those factors, even though they were not statistically significant, if you put in to adjust for all the co-variants, do you still get the same results, in a pure randomized analysis?

MR. HEDDER: I don't have the exact analysis, but we did do a logistics analysis with the co-variants at baseline and got much the same result.

DR. EHRENKRANZ: I have a slide of that.

DR. PACKER: It wouldn't address Rob's question anyway because you are adjusting for baseline covariants. These are differences that occurred post-randomization.

DR. CALIFF: Right, and we had two treatments, and one was high frequency ventilation and one was surfactant. It just so happens that both of those were used more frequently in the INO treated.

DR. EHRENKRANZ: Actually, they were both 70 percent in both groups, and 50 percent as pre-treatment modalities. This is looking at the data whether they got surfactants alone, high frequency alone, or whether both were needed.

In each case, the addition of nitric oxide onto previously therapies, nitric oxide clearly decreases the incidence of the primary outcome.

DR. LIPICKY: I wonder if you would comment on .006 is a pretty big number. Was your data safety monitoring

committee pretty trigger happy? That doesn't seem to be like a number I would have stopped the trial on.

DR. EHRENKRANZ: At the initial review -- I will give a little bit of an explanation but I will defer to Dr. Berger again.

They felt that if they could spare one child ECMO, that it was worth it. Do you want to further expound upon the timing of this?

DR. BERGER: The timing of the meeting was set. It wasn't a special meeting. It just so happened that at that meeting there were 190 or 195 babies that we had reported on.

At the time the meeting occurred, with pooling coordinators and finding out where babies were, I think we were into 215 or 220 that we could actually report to the committee.

The committee had discussed, a priori, setting guidelines and many of you are familiar with the values, and then it was crossed.

We told them, of course, that at the time 235 had been randomized, although we didn't have the outcome on the rest, and we had planned to go to 250.

I believe I can paraphrase the committee's summation and say that their concern was that waiting that much longer could impact on babies.

There are neonatologists and pediatricians and statisticians on the committee that felt it was inappropriate to wait any longer, because of the need for ECMO in these babies.

I think it is no different than the stopping of cardiovascular clinical trials on a single circumstance.

DR. LIPICKY: I think it is. Certainly it is not a bad number when you are looking at it. From my point of view because of the ECMO end point, it is not a very convincing trial.

DR. EHRENKRANZ: With all due respect, I doubt that with 250 it would have changed. I don't think those 15 babies -- I mean, we did some analyses to show, in the best and worst case scenarios, what would have been the relative risk, and I don't think it would have changed anything.

DR. LIPICKY: That is because you started out thinking you were going to do a P .05 trial.

DR. EHRENKRANZ: That is correct.

DR. LIPICKY: That is not a very suitable way to design a trial.

DR. EHRENKRANZ: Most cardiovascular trials, as I recall --

DR. LIPICKY: I disagree with that.

DR. EHRENKRANZ: We can argue extensively on that.

DR. PACKER: Let me suggest that this

philosophical issue will not be resolved today. We have not even scratched the surface here. What you are showing here are the nominal P values.

If you actually were pondering, according to events, modification of the no prime boundary, it is that boundary that is designed to protect an overall output of .05. If you cross that boundary, you expect that output at the boundary as .05.

DR. BERGER: What says is that the value is P less than .05. It wasn't actually calculated -- the P value has to be adjusted somewhat up or down depending on your outcome.

DR. PACKER: There is no known way of adjusting that P value. All we can say is that it is a nominal P value.

DR. BERGER: I think we are getting back into philosophy. I don't believe this trial was designed -- I spent 24 years conducting clinical trials and I would argue that this trial was conducted in every way up to the standards of most clinical trials.

DR. LIPICKY: Ten years ago.

DR. PACKER: Let me ask one question. You have provided a lot of information about other things that happened to these babies other than death or ECMO. In these slides that talked about the occurrence of other non-fatal

events, either during the period of study or during the period of follow up, you commented that you were struck by the significant degree of similarity, the frequency of events.

I guess I was disappointed to see that. If INO is so good or ECMO is so bad, that it is good to avoid ECMO, I would have liked to have seen fewer concombinant bad things that happened to the babies who got INO than the babies who didn't. Do you have any comment?

DR. EHRENKRANZ: Yes, we would have liked to also, but the major reason is that you are dealing with infants for whom the mean oxygenation index was 45.

These infants were extremely sick at the time they arrived. A lot of the outcome -- both CNS and respiratory and other problems -- was very much related to the severity of illness and the shape they were in before they were either started on nitric oxide or started on ECMO.

So, what our hopes would be is to -- what this is suggesting is that infants who are perhaps not as sick, who have lower OIs, may actually respond better -- not 100 percent -- but may respond better and perhaps we will see the kind of outcomes we would be coming from, less hospitalization, less chronic lung disease, and see this outcome.

DR. PACKER: Before moving to the next

presentation, let me just ask those on the committee as well as the presenters, to just keep in mind that the purpose of today's meeting is not the usual.

We are not here to determine whether the trials pass the usual, or whatever would be a standard for approval, because we are not here to judge approval.

We are really here to talk about design issues for further trials. Also, there are questions to the panel that ask us to judge the degree to which the evidence would convince us one way or the other, whether further study of this agent is warranted.

The degree to which we would normally ask questions about this trial probably needs to be subdued a little bit.

I guess to a similar degree, the degree to which the presenters go into the details of these trials probably needs to be subdued as well.

DR. LINDENFELD: This data implies that the OIs are not a very good predictor of who gets ECMO. I think someone in the audience suggested that wasn't the case, but this data certainly doesn't show very much difference.

DR. PACKER: Dr. Temple?

DR. TEMPLE: I just want to put two place holders down. I think the question of what the true P value is when you stop a study early is more complicated and surely must

involve, to some evolve, to some extent, on what the nominal value when you stop it is.

It is true, that it preserves the overall outcome. That doesn't mean that the finding at the time you stop is irrelevant.

It is a little like saying, if my critical value is .05 and I get .001 more, I can say it is less than .05. I don't think most people behave that way anyway. That is one.

The other thing is I think it is true that most trials are still designed, and they are still powered to have a nominal P value of .05.

That doesn't mean that that is a good idea, if what you are trying to do is rely on a single study, which may be what Ray was getting at.

I would not agree that standards are set for trials that are routinely powered to be greater. I would advocate that they do need power to be greater, and it is important that patients be informed of that, but that is a different discussion.

PARTICIPANT: I would like to make a comment about the previous question about this slide, pertaining to OI and ECMO.

What you have to understand, this is initial OI and these babies were randomized. Some of them got sicker

and met ECMO criteria. They started with an OI at 25 and then had ECMO at 40.

Some babies came in and met ECMO criteria with an OI of 60. They met ECMO criteria, and even if the OI came down to 25, we were still obligated to put those babies on ECMO, even though they responded.

I think this slide really does indicate that there is a better response at earlier OIs. I think it also represents how people at most centers -- I think at our center for sure -- stick to the ECMO criteria.

Even if we saw babies responding, and they still met ECMO criteria, we are obligated to give them ECMO.

DR. LIPICKY: One small question. How many of the babies in this trial had right to left shunts when they were entered?

DR. EHRENKRANZ: Seventy-eight percent.

DR. PACKER: Let's move on to the next presentation.

Agenda Item: Clinical Trials. Wessel.

DR. WESSEL: My name is David Wessel. I am a cardiologist and critical care physician trained in anesthesia, at the Children's Hospital.

We conducted a prospective randomized trial of inhaled nitric oxide for the treatment of PBHM among patients referred to a single large center, beginning with

our first patient in September of 1992.

Our objective was to systematically introduce this investigational therapy in a randomized fashion to all patients with PBHM, allowing for interim analysis and protocol for modifications until we, or others, could demonstrate sustained improvement in oxygenation, superior outcome with nitric oxide.

After two years, we analyzed our data, published the result, but continued to randomize patients with one important protocol modification, which I will discuss later.

All newborns referred to Children's Hospital with a clinical diagnosis of PBHM were eligible for enrollment. PBHM had to be confirmed with the patients breathing 100 percent oxygen and a PO2 less than 100 millimeters of mercury.

All patients were sedated and moderately hyperventilated. They received inotropic support for blood pressure and correction for acidosis was provided by bicarbonate infusion.

All of our patients had to have echocardiographic evidence of high pulmonary vascular resistance, and their gestational age was all 34 weeks or later.

We excluded patients with congenital diaphragmatic hernia, congenital heart disease, those patients with multiple congenital anomalies and those patients who had

echocardiographic evidence of low PBR.

So, you could have pulmonary hypertension, but if it is all left or right, then that is low pulmonary vascular resistant, and those patients were not included in this study, trying to get more at the issue of pulmonary hypertension itself.

After consent, we randomized our patients and recorded the baseline variables, which included the pre and post ductal oxygen saturation, arterial blood gas, ventilator settings.

Then we began inhaled nitric oxide in those patients who were randomized to receive NO at 80 parts per million, and the control patients continued on conventional therapy.

We repeated all the measurements I described, again, at 15 minutes, and then hourly for six hours, at 12 and 24 hours.

We reduced the inhaled nitric oxide to 40 parts per million at one hour, and then we had set weaning criteria. We weaned inhaled nitric oxide if the PO2 was greater than 60 and the FiO2 was .5 or lower.

Importantly, in this part of our study, we did not permit concurrent use of high frequency osculatory ventilation and inhaled nitric oxide.

It was possible to convert to high frequency

ventilation at the clinician's discretion immediately, but nitric oxide was discontinued during high frequency ventilation.

Discrete end points here were mortality, utilization of ECMO, oxygen dependence at the time of discharge from the hospital, and neurologic injuries in the form of seizures or intracranial hemorrhage.

Our continuous variables that we analyzed were oxygenation during the first 24 hours, oxygenation measured at PO2 over FiO2, and oxygenation index.

We enrolled 51 patients, but immediately identified two patients as being mistakenly enrolled. One of our patients had an echocardiogram taken a few minutes after he arrived and received a diagnosis of heart disease. The other patient had an erroneously written PO2. Neither of those patients received treatment under the protocol.

That left us with 49 patients, 26 for the INO group, 23 in the control. As you can see, they were similar in their age at entry, gestational, prenatal age, and the baseline PO2 is here, between 40 and 60.

Our analysis did not reveal any differences in terms of the associated diagnoses, the meconium aspiration being first, the idiopathic persistent pulmonary hypertension being second, and then pneumonia and more rare diseases, related diseases, being later.

If we look at the entire group of 49 patients in the first part of this study, you will see that the mortality rate is low.

This is an interesting point, because of the four patients who died, two had the pathologic hallmarks of what is known as lethal alveolar capillary dysplasia. This was found at autopsy.

A third patient had the clinical features of alveolar capillary dysplasia, but we were unable to obtain an autopsy on this child.

A third of our patients required ECMO. A quarter of our patients had either seizure or intracranial hemorrhage. Notice that none of these patients went home on oxygen therapy.

There were no differences between the two study groups in terms of mortality, use of ECMO -- eight in each group -- days on the ventilator or days on oxygen.

However, there were marked differences in oxygenation in this first part of our study. Here you will see the percentage change in PO2 over FiO2, shown on the Y axis, for the inhaled nitric oxide group shown in orange, and the control patients shown in blue.

This is compared to baseline, and this is a statistically significant difference also compared to the control population.

Similarly, we saw the desired reduction in oxygenation index in these patients at 15 minutes compared to baseline and compared to the control patient population.

This reduction in oxygenation was sustained over the first 24 hours. Here you can see the nitric oxide patients in orange, the reduced oxygenation index continuing below the baseline and is different from controls over several time points shown here, at six hours and 12 hours during the first 24-hour period.

The next slide shows that the PO2 in the patients who did go to ECMO improved in the patients who received inhaled nitric oxide, where those from 41 to the median value of 55, and improves compared to the PO2 and the oxygen saturation in those patients who went to ECMO in the control patient population.

The time to ECMO is not substantially different in the two groups, 2.5 hours in the control group and just over three hours in the nitric oxide group.

We speculated that perhaps better oxygenation may have helped with the tendency of intracranial hemorrhages and seizures to occur less commonly in patients receiving nitric oxide.

Here you can see that eight patients were affected out of 23 controls versus four out of 26 patients who received nitric oxide.

In summary, in the first part we saw that inhaled nitric oxide improved oxygenation compared to baseline, and compared to control during the first 24 hours.

We saw that ECMO use was no different between the nitric oxide group and the control group, at least within the limitations of the study design.

However, during the period prior to ECMO, patients on nitric oxide had better oxygenation compared to controls.

Nitric oxide patients had a tendency to have fewer adverse neurologic sequelae from PBHM.

Finally, we saw that mortality from reversible causes of persistent pulmonary hypertension is low in an ECMO center, suggesting that mortality may not be a reasonable variable to analyze except in very large clinical studies.

Now, there are obviously a number of limitations of this study. First of all, it is not a blinded study. There are no dose response data. It has low tolerance to detect small differences.

Perhaps most important, as Dr. Kinsella, Dr. Abman and Dr. Clark have told us today, the high frequency osculatory oxygenation strategy for improving recruitment was not utilized in the first part of this study.

We therefore published our interim analysis and modified our protocol simply to allow a concombinant use of

inhaled nitric oxide with high frequency osculatory ventilation.

Randomization continued. Here you will see the next 41 patients, the control group 20 patients, 21 in the INO group. Again, the age at entry and other baseline demographics are similar both between groups and compared to the first part of the study with the OI just at 30 or above.

Again, this is just the oxygenation index with the ranges shown in parentheses here. You see that there is indeed a reduction in this group also, very similar to the reduction in the oxygenation index that we saw in part one of our study.

However, notice that in the second part of the study we looked at the utilization of ECMO. There was a 55 percent rate of ECMO use in the control group that was reduced to a 14 percent incident in the inhaled nitric oxide group.

If we analyze that for ECMO as the outcome variable, again, we saw a significant reduction again for ECMO.

There was no difference in the days on ventilator or days on oxygen. We did not seem to prolong dependence on mechanical ventilation simply by virtue of giving inhaled nitric oxide.

If we combine the children from part one and part

two, there were 90 patients. We see that death, there is no difference between the two groups.

There is a significant reduction in the utilization of ECMO, and obviously the power of the second part of the study carried over to the entire group of 90 patients.

In February 1997, when we had apparently reached our initial enrollment prediction, we were under intense pressure from our clinical colleagues to examine our data in light of the published data that had just been in print from randomized multi-center trials.

An advisory panel of physicians of neonatology and critical care was convened. This included physician representatives from the Brigham and Women's Hospital, the Children's Hospital, the Beth Israel Hospital, the physician chairman of our ethics committee and members of the Children's Hospital committee on clinical investigations.

Their recommendation, after reviewing our data and reading the literature was that we should discontinue the randomization, but continue the nitric oxide protocol.

They felt that it was unethical to continue randomization in view of all available data. Thank you.

[Applause.]

DR. ROTHSTEIN: David, within your groups, for infants who were not placed on ECMO, was there any

difference in the time that they were ventilated to the time that to ECMO?

DR. WESSEL: No, they were virtually identical.

DR. ROTHSTEIN: Then the improvement in oxygen had no effect on the length of ventilation or the time to ECMO.

DR. WESSEL: That is right. I am also counting time on the ventilator as time on ECMO.

DR. ROTHSTEIN: The children who did not receive ECMO, the children who just stayed with mechanical ventilation, not ECMO.

DR. WESSEL: There is no statistically significant difference. We threw out the ECMO patients as part of our analysis, and then analyzed with respect to oxygenation, vasomechanical ventilation, et cetera, and they were the same. Those were not different.

DR. THADANI: The first part of the study did not show any difference between death or ECMO.

DR. WESSEL: Correct.

DR. THADANI: So, one could conclude that the fact that you used a different mechanism, you were driving the ECMO incidence higher. You could be harming the patients by your ventilation technique, so you are driving the ECMO incidence much higher in the control group than in the NO group.

DR. WESSEL: I am sorry?

DR. THADANI: In the second part is a very high incidence of ECMO, 20 patients, and in the first one there was no difference.

DR. WESSEL: I think eight out of 23 is very close to the 50 percent we saw in the second part. Perhaps there is a trend there that has not yet been revealed, but I think I would argue that the incidence of ECMO in the first part was very similar to that in the second part.

DR. LIPICKY: What was the incidence of right to left shunts in the data that you had?

DR. WESSEL: More than 80 percent. Part of it depends on whether you call bidirectional shunting evidence of left to right shunting.

DR. LIPICKY: The second question is, was this combined end point written down somewhere in the first or second or third draft of the protocol?

DR. WESSEL: The combined end point?

DR. LIPICKY: Of death and ECMO.

DR. WESSEL: The first draft of it was six months before the protocol began and it never changed after that.

DR. LIPICKY: So, that end point was in there.

DR. WESSEL: Absolutely.

DR. LIPICKY: The final P value for the combined end point?

DR. WESSEL: Of death and ECMO?

DR. LIPICKY: Yes.

DR. WESSEL: Was .12 for the whole group of 90, not for the second part.

DR. LIPICKY: The overall study result was what?

DR. WESSEL: Was .12 for the entire group of 90 patients with death and/or ECMO.

DR. LIPICKY: And .12 means you found something?

DR. WESSEL: No, I think that the committee that reviewed the data looked at part two of our study and knew that we had made one change in the protocol and had a reduction in death or ECMO that was statistically significant.

DR. LIPICKY: The second part of the study.

DR. WESSEL: Right. The original power prediction was for 90 patients. I thought for us to be intellectually honest, it was important for us to look at the entire group of 90 patients.

DR. LIPICKY: So, the entire study did not find it.

DR. WESSEL: For death or ECMO, we show improved oxygenation and reduction of the use of ECMO.

DR. LIPICKY: That is fine. So, the decision that you found something and it was no longer morally or ethically feasible to continue was based on a subgroup analysis of the whole trial?

DR. WESSEL: Right.

DR. LIPICKY: What was that P value?

DR. WESSEL: .04.

DR. LIPICKY: And that was uncorrected for multiple looks, because that whole data set had been analyzed before?

DR. WESSEL: Correct.

DR. LIPICKY: You had analyzed the first part of your study and that protocol end point was part of your preliminary definitions of what you were going to look for.

DR. WESSEL: Right.

DR. LIPICKY: So, it was at least your second look; maybe it was your third or fourth or fifth.

DR. WESSEL: It wasn't the third or the fourth or fifth.

DR. LIPICKY: It was at least two.

DR. WESSEL: We looked at the 90 patients two times. The decision, this is after the NINOS trial was out, the Roberts trial was out. There was a lot of information there.

We were still randomizing patients. There was a tremendous amount of heat in the community, both locally at Harvard Medical School and the faculty.

DR. LIPICKY: I just wanted to know what the facts were.

DR. WESSEL: I understand. These are ministers and lawyers along with many of the doctors on the committee, and they made this recommendation. So, that is where I had to go.

DR. THADANI: On that issue, you show in the overall trial there is no significant difference in either death or ECMO; is that correct?

DR. WESSEL: Right.

DR. THADANI: That means the utilization of the oxygenation index was of no value in predicting outcome; would you say that? You said there was better oxygenation with NO. Yet, it is not translated to outcome differences if you combine all the patients.

DR. WESSEL: There was better oxygenation, decreased utilization of ECMO.

DR. THADANI: Not if you combine the whole group. There is no difference. Not taking the second group and showing the differences, but if you put your boundary hypothesis of a 90-patient data base, there is no statistical difference between the two groups, either death or ECMO, irrespective of oxygen.

DR. PACKER: There is every possibility there is a power issue here and let's not make any more of that. There is no way that the hypothesis has either been proven or disproven based on the data which are available.

DR. SESSLER: I think it just makes a difference how you ventilate the patients. Can I just make that point? There are patient populations who receive one thing and there is a big difference.

In the spirit of Dr. Packer, we are here to try to learn a little bit more about that, and that is really the only reason I presented that data.

PARTICIPANT: One thing that I thought was really interesting was the fact that you had a substantial improvement in oxygenation with IMO, where as the incidence of ECMO use wasn't any less in the first study.

In the second part it changed dramatically. I guess there you again have a similar magnitude of improvement of oxygenation, but the use of ECMO fell dramatically.

Was there any change in the criteria or the threshold that you all used for instituting ECMO?

DR. WESSEL: That is obviously al very important question. We did look carefully, as best we could, at the OIs just prior to cannulation and in the other patients who weren't cannulated as well, to see if they were different in part two or part one. They weren't.

I think in an unblinded trial there is a possible bias working both ways here. In the first part, if you drag your feet another 30 minutes, things might change.

We have an ECMO group that was intent on, when you meet criteria, you get cannulated. They would hover, you know, until we had two successive OIs that were above 40.

I think we were able to look at the reason of -- what was different. Was it just high frequency ventilation? Their oxygenation was better and therefore they didn't get ECMO and that is really the bottom line.

DR. CURRY: I think the answer to that question, to my eye, randomly there was a markedly significant difference between those two groups in the first 20-something patients with a CO2 difference of 20, 60 versus 40, if I am remembering right.

If you were strictly going by the qualifying criteria, that blunted the need for ECMO. There was an unfortunate difference in the groups.

On analysis I think it was again a power difference. It wasn't statistically a difference, but we had a PO2 of 47 in the NO group and a PO2 of 64, I think, in the control.

DR. WESSEL: In the world of ECMO, that is significant.

DR. CALIFF: Two questions that are not easy questions. You are convinced that changing the mode of ventilation made a big difference in the result.

Your statistical end points for that, did you do

some kind of test for interaction?

DR. WESSEL: Yes.

DR. CALIFF: That was?

DR. WESSEL: I don't have the curve, but we did a regression analysis looking at probability of ECMO versus entry OI for the four kinds of therapy -- conventional, high frequency, conventional with nitric, high frequency with nitric.

The group that comes way out to the right with reduced probability is high frequency with nitric oxide, statistically significant from all the others.

We did do a regression analysis looking specifically at this issue.

DR. CALIFF: The second question -- this is really a tough one, but we are in an era where we are going to try to understand how to treat children.

I get a sense that there is a belief that the criteria for stopping trials with children should be different from the criteria in adults. Do you have an opinion on that?

DR. WESSEL: I think that is a little bit of a philosophical question.

DR. CALIFF: But it is a key question.

DR. WESSEL: It is. Those are the facts on the last slide. If I were as scientific as Dr. Lipicky, I might

have jumped up and down and said, this is wrong; this is wrong.

I can tell you that I did say that a year before when these other data first came out. I think that the answer to your question that, if possible, the criteria for stopping trials is different, but I am not the person to say if that is right or wrong.

DR. PACKER: Let me follow up on that. We have questions before us from the agency to address the issue of further trials with NO.

You are coming from an experience where a duly empaneled committee of non-involved physicians and IRB chairmen advised you to stop what you were doing, based on the data that you showed them and showed us.

Based on your own personal view, do you think that further trials with inhaled nitric oxide are unethical?

DR. WESSEL: I think that further trials that randomize patients to placebos are unethical. I believe that there are other ways to do trials that can give us more information.

I think having a placebo-controlled trial for this disease, with well-selected patient populations would not be ethical.

DR. PACKER: If the data that you have shown us, although it may have been persuasive to your ethical

committee, is not persuasive from a regulatory sense, how would you design any further studies to demonstrate that this agent was effective for anything?

DR. WESSEL: I think there are a couple of ways to do that. First of all, I think we can spend three minutes at the end, and I will have a few slides to summarize at the end, looking a little bit at a meta analysis.

You will see that these trials are different with different people but they have end points that are similar and there is some validity in doing a meta analysis in 538 patients. I think we need to look at that.

Then I think we need to think about alternative ways to do trials. One of the trials is, even though it won't give us a long-term safety issues, is to do a cross over trial.

Perhaps as the NIH group are suggesting, do a nitric oxide trial for those patients who have an OI under 25, whereas anyone over 25 is not in a randomized trial.

We can do randomized patients in certain categories where we cannot say with the same degree of confidence that this is a good drug.

DR. PACKER: A cross over trial using death or ECMO as a primary end point? That sounds hard to do.

DR. WESSEL: I would say that first of all, you can have a non-randomized trial with OIs less than 25 that

does not cross over. Personally, I think that could be designed.

I think that is much harder for children who have a high probability of dying if they don't get cannulated for ECMO now. I think that would be a much more difficult trial to have a placebo-controlled group.

DR. PACKER: Okay, why don't we proceed to the next presentation.

Agenda Item: Clinical Trials. INOSG.

DR. ROBERTS: I am Dave Roberts. I am a neonatologist and a staff anesthesiologist at Massachusetts General Hospital.

I am here to present the results of a trial whereby we tested whether there was a difference between oxygenation in full-term infants with hypertension in neonates.

There are several studies that inhaled nitric oxide is a selective vasodilator. So, we tested that in full-term newborn lambs.

We referred them at term from a Cesarean section, anesthetize and ventilate them and were able to add catheters, by which we could measure pulmonary artery pressures, and ultrasonic throat probes by which we could measure blood flow of these newborn lambs.

We then obstructed their pulmonary circulation by

having them breathe at oxygen up to a level of .1, which acutely increased pulmonary pressure.

In this lamb, it changed the blood flow from left to right, to here right to left. As you can see, with the introduction of nitric oxide into the ventilator, despite continued hypoxia, there was a rapid reduction in the pulmonary pressure, reversal of the blood flow, and there was no systemic drop in aortic pressure and the blood flow went back to preliminary control levels.

When the nitric oxide was discontinued, despite still breathing oxygen, there was rapid recovery of the vasopulmonary constriction.

When one does a dose response curve in these newborn lambs with hypoxic pulmonary construction, if you look at the pulmonary vascular resistance to with increased 10 percent oxygen breathing, there is a significant reduction in pulmonary vascular resistance at 25 parts per million, maximum reduction at about 80 parts per million.

Despite breathing 160 parts per million of nitric oxide, there was no drop in systemic vascular resistance.

So, this suggested that nitric oxide is a selective pulmonary vasodilator in the newborn pulmonary circulation.

With this information, at Massachusetts General Hospital we performed a trial of inhaled nitric oxide in

babies that were referred to our center for ECMO.

We were able to introduce nitric oxide into the ventilator prior to the cannulation of the babies.

As you can see here, when we look at PO2 levels, there was no difference in decreasing the FiO2 level from 1.0 to 1.9 to make room for the inhalation of nitric oxide.

With inhaling 80, 20 and 40 parts per million of nitric oxide, there was a significant increase in the post-ECMO PO2.

So, in this pilot study it suggested that nitric oxide might be important in increasing systemic oxygen levels in infants referred for ECMO because of TPHM.

So, as a result of that, we generated a hypothesis that inhaled nitric oxide could increase systemic oxygen levels as conferred with conventional inhalation without nitric oxide.

In addition, inhaled nitric oxide would not importantly increase systemic blood pressure levels.

The way that we approached this was through a multi-center sort of design, where it was prospective, randomized and placebo controlled and there was a double blinding occurring in this design.

A number of centers were involved, including San Francisco, Buffalo, Dallas, Connecticut, Chicago and Philadelphia.

We included full term babies with persistent pulmonary hypertension in the newborn, as diagnosed by echocardiogram.

In addition, they had to have severe systemic hypoxemia, as defined by a PO2 of less than or equal to 55 millimeters of mercury obtained over a half hour period of time while they are breathing FiO2 1.0.

We excluded babies who had previous treatments with ECMO or high frequency osculatory agents, as well as those with a congenital diaphragmatic hernia or suspected lung hyperplasia, congenital heart lesions aside from a PEA and PFO, those who had hypertension, polycythemia, unevacuated pneumothorax or a phenotype consistent with a chromosomal abnormality.

Babies who had previously been treated with exogenous surfactant but still had systemic hypoxemia were enrolled in a parallel study, but their data was kept separate until after the interim analysis was performed.

There were two phases for this study, an acute treatment phase and a chronic treatment phase. During the acute treatment phase, the first step was to evaluate the effects of decreasing the FiO2 from 1.0 to .9, to allow for treatment with either nitric oxide gas or equal flow nitrogen gas, the control gas.

If, after decreasing the FiO2 from 1.0 to .9, if

after 10 minutes the CO2 did not decrease by 15 percent or was greater than or equal to 25 millimeters of mercury, they put them on then to be treated with treatment gas.

The treatment gas consisted of either zero or 80 parts per million of nitric oxide in nitrogen. After 20 minutes period of time, a blood gas and a blood pressure were obtained.

A gas was considered to be successful if it increased post-FiCO2 of greater than 55 millimeters of mercury, decreased oxygenation index of less than 40, and also having blood pressure greater than or equal to 40 millimeters of mercury. This is what defined a successful treatment.

During the cross treatment phase, the inhaled nitric oxide or nitrogen was continued at a lower level in a blank fashion.

It was decreased twice daily. If the oxygenation index was greater than 40, then the patient would exit the study.

The FiO2 ventilation was removed as per usual clinical practice, and the decision for ECMO was up to the physician caring for the patient, and was determined in a blinded fashion using the usual criteria.

Now, we had a safety and monitoring committee which consisted of three members. The first task was for

them to look at the results whenever we had 20 patients involved.

It confirmed the assumptions that we used in our initial analysis. At that time it was planned that we would do interim analysis when we reached 50 and 75 patients, and we would stop the inhaled nitric oxide if the systemic oxygen significantly increased when compared to the control gas.

Now, we performed the first analysis at 50 patients and at that point inhaled nitric oxide was found to importantly increase the systemic oxygen levels, without decreasing the systemic blood pressure.

It was decided to stop the study at that point. At that point there were an additional eight patients who had previously been treated with surfactant.

The data combined for these patients, for a total of 58 patients, were combined for the analysis.

As you can see here, in those who received the control treatment versus those who received inhaled nitric oxide, there is no important difference in the gestational age, the birth weight, number of males and females, the APGAR scores, the incidence of meconium aspiration syndrome, unevacuated pneumothoraces, or bacteremia that were obtained.

In addition, there was no important difference in

the type of baseline ventilator or blood gas values in the control or patients who had received inhaled nitric oxide.

I want to highlight here that all the patients had severe systemic hypoxemia, despite breathing in 100 percent oxygen when the baseline ventilator and blood gas values were obtained.

This corresponded also to an oxygenation index that was 46 in the control group and 43 in the inhaled nitric oxide group.

This is a look at the short-term effect of inhaled nitric oxide on systemic oxygen levels. It is baseline versus 20 minutes after treatment.

The control group are shown by the light blue boxes and the orange boxes are inhaled nitric oxide. As shown here, there is no significant difference between the two groups at baseline.

However, after treatment with inhaled nitric oxide, there was a significant increase in the post-FiO2 level.

This corresponded also with a decrease in the oxygenation index, as shown here. There was no difference at baseline oxygenation index between the two groups, and with inhaled nitric oxide treatment, there was a significant reduction in the oxygenation index.

As far as looking at the incidence of ECMO, as

shown here, the percentage of patients in the control group who did not receive ECMO was only 29 percent. For those in the inhaled group, 60 percent did not require ECMO treatment.

This is a profile of patients who were breathing inhaled nitric oxide, to look at the effects on the oxygenation index over the days of treatment.

As you can see right here, for patients who were breathing inhaled nitric oxide, again there was a decrease in OI, and this persisted throughout the treatment course. The longest course was eight-and-a-half days for these babies.

Seventy-five percent of the babies who had an initial response of a decreased oxygenation index persisted throughout the treatment.

This is a profile of the proportion of patients who were inhaling nitric oxide. As you can see, about half the patients were off nitric oxide by about two days of treatment, and the longest treatment, as I mentioned, was eight-and-a-half days in our patients.

This is looking at the inhaled nitric oxide level, the median methemoglobin level in patients breathing inhaled nitric oxide.

As you can see here, whenever we were able to decrease it twice a day, there was a significant reduction.

By two days they were down to about 20 percent. Again, it went out to about eight-and-a-half days.

The median levels are shown here. The one baby who was breathing 80 parts per million had a significant increase in his methemoglobin level, up to 18 percent. That subsequently decreased, as the inhaled nitric oxide level was able to be decreased as per protocol, and with treatment with vitamin C.

Nevertheless, despite that hemoglobin level, there was no systemic acidosis in that patient.

Now, criticisms for the use of inhaled nitric oxide is that with ECMO you could rest the lungs, go to a lower FiO2 requirement, use less pressure, perhaps have less trauma. With inhaled nitric oxide, with the increase in post-FiO2 oxygen levels, you would still need to ventilate them, perhaps with high levels of oxygen and pressure.

What we did in this analysis was to compare babies who were in the control group -- that is, were not treated with inhaled nitric oxide -- but who did receive ECMO, with those babies who had successful treatment with inhaled nitric oxide without ECMO, looking at the number of days of ventilation, oxygen, and hospitalization.

As you can see here, there is quite a bit of variability within the group.

Looking at them, there appears to be no big

difference in the number of ventilation, oxygen therapy or days of hospitalization, and those treated with ECMO or those treated with inhaled nitric oxide alone.

As a result of our study, we promote an acute inhaled nitric oxide treatment. It increases systemic oxygen levels and it does not appear to fully decrease systemic blood pressure.

Chronic treatment with inhaled nitric oxide appears to decrease the requirement for ECMO and does not increase methemoglobin levels. Thank you.

[Applause.]

DR. PACKER: Just a quick question. I know the ECMO analysis is post hoc. Did you do a post-hoc analysis of death plus ECMO, given the importance of always defining outcomes with the ECMO?

DR. ROBERTS: We did not make that end point in our trial. However, that was made in looking at our data post-hoc.

They found, from what I understand, very similar differences with inhaled nitric oxide decreasing that post-hoc.

DR. PINA: I think early on this morning we were hearing there were some differences in centers as to the criteria for using ECMO.

You started off by saying that these patients had

been referred to your institution for ECMO because they had met criteria wherever these children were before.

Once you receive these children, do you have any data as to how different your ECMO criteria was from the criteria at the other centers? In other words, would they have met the same ECMO criteria at your center?

DR. ROBERTS: I think what I was referring to is that the babies were referred to our center for ECMO. That was during our pilot study.

During our control study, multi-center study, a number of those babies were actually inborn, and were not referred in.

Now, there has been some talk about a variation in ECMO criteria in each center. We do not believe that we could get a group of neonatologists in one room and decide what would be the optimal levels to choose prospectively.

What we chose to do in our study was to maintain the blind of the treatment, and let them use the institutional requirements for the definitions at that point, with the assumption that there would be very little bias for the institution with ECMO, based on whether or not there had been previously inhaled nitric oxide or control treatment.

DR. GRINES: I am a little confused about the hemodynamic responses to inhaled nitric oxide. Apparently

the pulmonary artery vasodilators that many of these other articles commented on how the wedge pressure goes up with therapy.

I was wondering whether some of the responses were due to the elevation of wedge pressure.

DR. ROBERTS: Well, we typically don't measure wedge pressure in babies. I would presume that a number of them did not have that failure. So, the incidence of wedge pressures would not be high. I am not sure where vasodilation occurs in inhaled nitric oxide.

DR. GRINES: I think I saw your earlier slides, when you were showing animal data, there was actually a drop in arterial blood pressure but the FBR remained identical. Wouldn't you assume that there would be a drop?

DR. ROBERTS: That is a very interesting thing to pick up on. Let me go back to that. Are you referring to this one?

What I think you are referring to, perhaps, is here is we have them breathing from .21 to 2.10. As you can see, just looking at flow, this is an ultrasonic flow probe put in the thoracic aorta.

There is actually an increase in blood flow to the lower carcass. It is very interesting that with nitric oxide inhalation there is a reduction in blood flow.

I am not sure why this occurs. It is very

interesting to me, but it did seem to be something that we saw here.

Looking at pressure itself, there was really no change in systemic pressure with nitric oxide.

DR. GRINES: Did you find that in your babies?

DR. ROBERTS: What we did do was, we defined prospectively a drop in blood pressure where the mean would be less than 40 would be significant, and we used that as our composite end point when we looked at the definition of success or failure.

We did measure -- record -- mean blood pressures. It was interesting that whenever there was a decrease in the FiO2 from 1.0 to .9, there seemed to be a little decrease in the mean blood pressure.

The majority of the decrease was during the initial decrease in the FiO2. Then, with going on and starting inhaled nitric oxide, there was very little change, I think only a change of one millimeter mercury pressure in the mean pressure.

DR. GRINES: The final question is -- I think Dr. Lipicky was referring to this -- how much of a change on oxygenation could be do to alteration of the shunting, versus actual alterations in oxygen uptake.

DR. ROBERTS: I do not know that from our data. We did not collect information about the number of babies

who were bidirectional versus who got the shunt. I do not know that information from our data.

DR. GRINES: I wonder if any of the other presenters do?

DR. WESSEL: I do.

DR. PACKER: Could you repeat the question?

DR. GRINES: It seems like all these babies have a right-to-left shunt. A lot of the differences in oxygenation could be due to the differences in shunting.

DR. WESSEL: That is an absolutely correct analysis. We think and hope that much of the alleviation of hypoxemia is due to taking away the right to left shunt, especially for ductus arteriosus.

With respect to the ductus arteriosus, the changes in pulmonary blood flow that one sees can simply represent the reversal in blood flow across the ductus in the neonatal lamb model.

We have studied it in a number of newborns and other children, after cardiac surgery and in the cath lab. I think we can say with confidence that inhaled nitric oxide does not lower cardiac output.

It does not raise the wedge pressure in these kinds of situations. It might in severe methestenosis. It certainly doesn't lower the cardiac output in some children who are very severely -- remember, many of these babies have

super-systemic pressure in the pulmonary artery. It can reduce the outflow of the right ventricle.

It proves much different and more dramatic than the adult ARBS patient population. We have had patients with systolic pressures in the area of 130 millimeters of mercury, and we have the data for over 500 patients with PA lines in, measuring outputs. We chose not to present those, I gather, today, but I would be happy to get you that, with direct measurement.

PARTICIPANT: I have studied the newborns with echocardiography before and after, and also crossed over. I can't say that the hemodynamic changes that are proposed do occur, but whether they have a closed vectus or an open vectus arteriosus, there is an improvement.

It is possible that there is a slight decrease in cardiac output because of the decrease in oxygenation. We can also say that the patients who crossed over and had an IO over 40, that the reason they crossed over was because they had the shunt increase.

DR. GOLDSMITH: As opposed to the previous study, you achieved your results using conventional ventilation. Was there any strategy that was used, is there any specific strategy from Dr. Wessel in terms of rib expansion or other things that make a difference in terms of using osculatory ventilation?

Why do you have your results with conventional and Dr. Wessel could not achieve this?

DR. ROBERTS: Well, at the time we started this study, which was back in 1992, we tried to really minimize the amount of variability prior to enrollment in this study.

For that reason, we got rid of all the patients who had lung hyperplasia or other forms of congenital heart disease.

At that point, there was a lot of data suggesting that HIFB was very efficacious and very important for recruiting.

At that point, we decided as a group to not include those babies because of the variability that that modality might impart on our results.

So, what we did is, we chose to use conventional ventilation. We did not in advance set any kind of criteria for ventilation or any kind of goals along those lines.

We just let whatever was being done in clinical situations be the determinant prior to randomization.

DR. WESSEL: I think Dr. Roberts said there may be fewer patients who had pulmonary parenchymal disease that would be addressed by that recruitment strategy.

Also, in the study that was presented, the PO2s were lower to begin with. You had to have a PO2 of 55 to get into the study, where in our study you had to have a PO2

under 100.

So, I think there are some differences that may reflect what the underlying disease was, where a high frequency ventilatory strategy may be more applicable in one population than the other.

DR. LIPICKY: The incidence of shunts in the kids in your study?

DR. ROBERTS: We did not stratify that.

DR. LIPICKY: So, you do not know.

DR. ROBERTS: That is correct.

DR. LIPICKY: But you know they all had pulmonary hypertension?

DR. ROBERTS: Yes.

DR. LIPICKY: How did you know that?

DR. ROBERTS: They had bidirectional shunting or directional shunting. But I don't know the number of patients that had right to left.

DR. PACKER: Okay, before we go on to the next presentation, just to clarify one question to Dr. Wessel, your final presentation, the clinical summary presentation will be presumably on a number of combined analyses across the trials; is that correct?

DR. WESSEL: Yes.

DR. PACKER: Given the nature of today's hearings -- that is, it is not for approval or non-approval, given

the fact that the committee has not attempted to analyze any of the individual issues, I think we will probably be best off if we skip that small summary and went on to the next presentation on the Ohmeda trials and make that the final presentation.

DR. WESSEL: Let me point out that there are only three slides on the trial summary, and we can skip those. It does summarize the feeling of at least the presenters with respect to very important issues with regard to appropriate end points and conclusions and opinions.

DR. PACKER: Okay, three slides.

Agenda Item: Clinical Trials - Ohmeda 01/02.

DR. STRAUBE: My name is Richard Straube. I am a pediatrician hired by the company formerly known as Ohmeda. I am going to be presenting the results of a multi-center trial.

This trial was originally designed as two phase B trials which had identical -- this was a randomized, placebo-controlled double-blind trial which enrolled full-term infants with cardiographic evidence of pulmonary hypertension.

Patients had to have a PaO2 of less than 100, breathing 100 percent of O2 and had to be less than 72 hours of age.

Patients received either a nitrogen placebo or 80

ppm of INO. The prospective defined end point of this trial was one of the following four bad outcomes: death, ECMO, neurologic damage defined as either seizures or intracranial bleed, bronchopulmonary dysplasia.

When this trial was initially designed in 1992, there were two new treatments that were beginning to be used.

They had no evidence of efficacy and were felt to potentially have some sort of adjuvant effect, and so this trial elected to exclude any patient receiving surfactant or high frequency osculatory ventilation.

All patients were standardized on the infant star(?) ventilator and used the same delivery device.

The trial was originally scheduled to enroll 320 patients. Unfortunately, during the conduct of the trial, the use of surfactant and high frequency became much more frequent and enrollment dropped rapidly.

Then with the announcement of the NINOS data in early 1996, our enrollment fell to approximately two patients a month, and we elected to halt the trial when 155 patients had been enrolled.

There were approximately 40 patients in each of those groups. Patients were approximately 24 hours of age at the time they were enrolled. The PaO2 was approximately 60 on 100 percent oxygen and the OI was about 25.

The patients in this trial compared to the NINOS trial were a little bit younger and a little bit less ill at the time of randomization.

When INO was started, the O2 increased dramatically with the NO, went up slightly in placebo. The difference both from baseline as well as the difference between placebo and the NO was statistically significant. P was .001, and this was maintained for four hours.

Similarly, the change in oxygenation fell more dramatically in those receiving NO than in those who received placebo and, again, this was maintained.

Looking at the primary end points in this trial, they were a composite of what we call PPHN major sequelae. It decreased 59 percent for the placebo group, 52 percent for the NO. This was not statistically significant. As you can see, there was no dose response apparent.

We also looked at a post hoc analysis of death and ECMO in this trial. Again, this was a reduction from 37 percent down to 28 percent with NO. This 24 percent reduction was similar to that seen in the other trials. Again, because of the size of the trial, this was not statistically significant, and again, no dose response was seen.

Adverse events were collected and the types and frequency of adverse events with similar dose groups, there

were no significant increases with the exception of methemoglobinemia.

Thirty-three of the 37 patients receiving 80 ppm had methemoglobin levels above seven percent.

We standardized the measurements of methemoglobin by using the same brand and model of cooximeter to measure it, at each of the 25 sites that participated in this trial.

As you can see, there is a nice dose dependent increase in methemoglobin from placebo by 20 to 80. In those patients receiving the 5 and 20, however, methemoglobin rarely went above two percent. In those patients with 80, there were a substantial number that went high.

Again, those patients who had greater than seven percent methemoglobin had the dose of inhaled nitric oxide reduced or discontinued.

Similar findings were found when we looked at NO2 levels. Again, placebo 5 and 20 at very low levels throughout the course. However, those patients did have substantially higher levels of NO2 measurement.

A summary of the acute data, the trial was halted prematurely and therefore had insufficient power for the efficacy analysis proposed.

There was an acute response to inhaled nitric oxide, decreased incidence of ECMO. However, this was not

statistically significant.

The acute NO appeared to be safe and well tolerated.

In addition to our acute follow up, we had prospectively planned that all patients would be seen at 12 months of age for follow up.

Of the 155, 100 of those patients, 92 percent of the patients we have vital status and approximately 80 percent neurologic data, somewhat smaller numbers of patients who had complete audiology done.

We had no late deaths in this trial. There was no statistical difference between the two groups with respect to deaths, no dose response.

Similarly, if you look at those patients who were evaluated by a pediatrician, looking whether they had no new neurologic abnormalities, we see very similar distribution, no difference between placebo and pool and no dose response.

Similar findings were seen with cerebral palsy, which was a specific type of neurologic abnormality which was examined for, no difference between placebo and focus.

Similarly, looking at hearing, looking at no hearing abnormalities, mild or major, no difference between placebo and pooled, no dose response.

Looking at motor performance, again, very similar numbers of normal motor performance in the placebo versus

pooled, no dose response.

Overall, physicians were asked to asses the condition as normal, mild impairment to severe impairment. No difference in distribution between placebo and pooled, nor was there any dose response.

In summary, we have follow up data on between 70 and 93 percent of the patients and there is no difference looking at these patients at one year of age with respect to mortality, developmental delays, hearing abnormalities, and no lung dysplasia. Thank you.

[Applause.]

DR. PACKER: Let me begin, just two quick questions. The medical reviewer notes that in this trial, at the end of one year, 14 percent of the patients in the control group were taking ambulatory oxygen -- no, 14 percent of the patients in the NO group were receiving ambulatory oxygen versus zero in the control group; is that correct?

DR. STRAUBE: Yes.

DR. PACKER: In his review he questions what the significance of this might be. He suggests the possibility that this may be a long-term manifestation of the toxic effect of NO potentially through NO2. Do you have any comments?

DR. STRAUBE: Yes. First of all, I think the

numbers are very small, so it is hard to draw too much significance from that.

Second of all, if you look at the actual duration of treatment, it was substantially lower in those patients receiving NO. So, although there were more patients, most of them were on it for much shorter periods than those patients in the control group.

DR. PACKER: Let me ask. If you use the composite here which is more comprehensive than the composite that has been used in other trials, this composite is that ECMO neurological sequelae and bronchopulmonary dysplasia, based on the conversations we had earlier, we think that more comprehensive ECMO/mortality data may have the advantage over less comprehensive measures.

At least three of the four components are measures of direct clinical outcome as opposed to ECMO, and that was a prespecified primary end point.

DR. STRAUBE: That is correct.

DR. PACKER: The effect on that primary end point was not statistically significant. Based on these data, do you think that further clinical trials, placebo controlled trials, with this agent are unethical?

DR. STRAUBE: Based on this trial, no. Based on what we have heard today, yes.

DR. PACKER: Let me ask a question. For what

reason would you think that the results of other trials that we have heard today should be held in higher regard than the results of this one?

DR. STRAUBE: This trial was halted prematurely, with less than half the patients anticipated actually enrolled in the process.

I also think there may have been a certain amount of selection bias because we were excluding all patients receiving surfactant and high frequency.

I think that criteria probably changed over the three years that this trial ran. I am not sure how representative these patients are.

DR. PACKER: But this was a double blind, placebo-controlled trial.

DR. STRAUBE: Yes, it was.

DR. PACKER: Which has substantial design advantages over some of the open label experiences we have heard about.

DR. STRAUBE: Yes.

DR. PACKER: Yet, you would count those and put more emphasis on those than this?

DR. STRAUBE: I think that you have to look at the evidence as to whether or not there is benefit from this therapy.

DR. RODEN: Can I ask you or someone else to

comment on the lack of dose response relationship, specifically the possibility that there is a mechanism of action with this compound with some sort of beneficial effect that is dose related and the classic effect that appears at higher doses, that created a U-shaped dose response curve?

DR. STRAUBE: Certainly in our trial there was a lack of dose response. I think that is compatible with the fact that you have achieved all of your responses at the lowest dose tested.

Certainly some of the data which was presented this morning would suggest that there is a point at which at least in pulmonary selectivity for NO vasodilation. There is data which saw clearly that if you get too high doses, even poorly ventilated areas, you get enough NO to get some vasodilation.

Then you begin to lose the interests of the AO2. So, I think yes, you can go too high and lose some of the selectivity.

DR. GOLDSMITH: A comment on stopping this study prematurely. Again, back to what I mentioned earlier, the demographics of babies being born in this country and getting to ECMO centers where there is the INO protocol.

Generally, by the time the baby gets to these centers, it is the first hospital they have been in the

first 24 or 48 hours of their life.

They are born in a community hospital. They are sent to an NICU which is one out of four hospitals in this country. Then they are sent to an ECMO which is one out of fifteen.

By that time, they have gotten high frequency ventilation, surfactant, or anything the neonatologist could have thrown at them in the first two hospitals.

The old thing that if your only tool is a hammer and the problem looks like a nail, these babies get all kinds of therapies before they get to someplace that they can be randomized.

The problem is, in getting these babies in, the babies who were received at the centers, to start INO, were automatically excluded because they had been on high frequency, many of them had received surfactant and the technology is changing quickly.

So, the question you asked, can we hopefully go ahead and do a randomized study in the future, has to take into account the demographics of how these babies get to centers where they can be randomized.

Eighty percent of the babies you have seen today, all 500 of them, were not born in the centers in which they were entered.

DR. PACKER: That is a generic issue that affects

all clinical trials of any indication regardless of whether it is this agent for this indication, trials done in specialized centers.

Patients have to get there somehow. There is always a selection bias. You can only study the patients that you see. But then, you can only evaluate the data that you get.

DR. CALIFF: I want to follow up on your vascularization here. What I have heard, my understanding of the contention is that the only advantage of NO is that it reduces the need for ECMO. There is no demonstration of any other clinical benefit.

We have really no main -- if we believe that children, in fact, are not just small adults, they are developing organisms and we have a therapy which has the potential to have long-term harm, and we have no convincing evidence about the long-term effects, I am trying to understand the ethical balance between a demonstrated clinical benefit -- which I am convinced of -- and the relation of therapies on large numbers of developing organisms, not understanding what the long-term consequences of that therapy might be.

I am concerned that we are holding children to a different standard than adults and continuing this tradition of using therapies for children that are unheard of from the

perspective that we normally use therapies.

I am kind of lost on that perspective. I would be interested in your point of view on that.

DR. CLARK: I would like to just echo that and say there are still two large multi-center trials that are randomized for patients. I would argue that those have been reviewed carefully and discussed in open forums.

Just to offer a balance, not every institution in the country has decided that is unethical.

DR. PACKER: While you are there, I guess when one looks at the long-term outcomes -- and they are very similar in all the randomized trials -- it would appear that -- and I will echo what Rob has said -- that the outcomes here are very, very similar.

We are not talking about anything here which, if one went one pathway and one another, would result in a difference that was irreversible.

It is really a decrease in the utilization of a procedure, although a very awful procedure. It is still a decrease in the utilization of a procedure which, if the children have that procedure, it may be an awful experience, but their outcomes aren't any worse than the children who don't have that procedure.

DR. GOLDSMITH: When you say long-term outcomes, though, you are talking a year or two in terms of

neurodevelopmental and bronchopulmonary dysplasia.

Nobody yet, to my knowledge, has yet looked at the mutagenicity, which we heard about from Dr. Abman earlier. We have been down that road before, in terms of the effect of things like peridactylnitrates on the lung. We don't have any information on that.

DR. PACKER: I think their impact may be more reason to be concerned. I guess I am just struck that there is no particular reason -- no trends to benefit.

DR. KONSTAM: Can I just follow up on Rob's remarks? I agree very much with the implication of the remarks, so I am not clear about this ethical story either.

Just to balance it a little bit, I am not sure that we are any more -- I don't think we are any more convinced about the long-term safety of ECMO as compared to the long-term safety of inhaled nitric oxide.

So, in thinking about the implication of your question and going forward with it, I guess I wouldn't want to go forward with it holding inhaled nitric oxide to the standard of proving that it is as safe as ECMO, because we haven't proved ECMO.

In other words, it is a balance. I guess the same comments that you make would apply to ECMO as well.

DR. CALIFF: There is one big difference, and that is that ECMO is proven to save lives. It would be hard to

randomize for that.

DR. PACKER: But in terms of efficacy, if ECMO is proven to save lives, and if you accept -- we haven't really talked through the data here -- but if you get convinced that use of nitric oxide reduces the use of ECMO with no difference in mortality -- there are a bunch of ifs to that -- if you did that, then you might infer that perhaps nitric oxide saves as many lives as ECMO, or is equally efficacious without the morbidity associated with ECMO.

That is a line of reasoning that you could follow. You would still be left saying there is a lot about the potential long-term toxicity about inhaled nitric oxide that we don't know.

All I would balance that against is that there are probably a lot about the long-term adverse effects of ECMO that we don't know.

DR. SESSLER: I think your comments are on target, frankly. I think that we may undervalue the fact that we have now ECMO-free survival.

We have got no change in mortality rate in some of the larger studies, with a significant reduction in the utilization of a technology that has been pretty convincingly proven that it improves mortality.

So, I don't think we can toss that out as inconsequential. I think it is something that is pretty

difficult to prove, given that ECMO has achieved its place in the management of these patients. I think that is something that is well worth looking into in terms of its value.

DR. LIPICKY: I just want to, before I lose track of it, ask you in your trial what the incidence of right and left shunts was.

DR. STRAUBE: Five percent. Everyone had pulmonary hypertension.

DR. LIPICKY: So, why do you pick on ventilatory assistance as being the difference? It seems like the hemodynamics in your kids was different than in all of the other studies.

One of them had 78 percent right and left shunt and the other one had 80 percent. Were these the same kids?

DR. EHRENKRANZ: One of the differences is that the echocardiograms are generally done one time in the 24 hours prior to beginning nitric oxide.

They may be done in our study up to 24 hours. In some of the studies they were done within an hour.

One of the things that we wanted to exclude was cyanotic congenital heart disease.

So, this is a very changing disease. What may be present at 8:00 o'clock this morning when we first begin to evaluate a patient may be differing later tonight.

DR. LIPICKY: Are you saying that the difference in the incidence of right and left shunts in the studies was changed?

DR. EHRENKRANZ: The presence of a regular shunt, the presence of pulmonary hypertension was gauged on a number of different parameters.

The cardiologists did the echocardiograms. They looked for bidirectional shunting, they looked for right to left shunting. They also gave their own assessment of whether they felt that there was enough data collectively to indicate that there was pulmonary hypertension.

The baby, at the time that they might actually study gas, the first one, when these kids come in -- at least in our study, the first thing that was done was not to put them in the study.

We stabilized them. We manage them. Part of their evaluation was, do they have cyanotic congenital heart disease.

Part of that analysis is, do they have pulmonary hypertension. They may not have had another echocardiogram. They may have had no evidence of pulmonary hypertension at the time of that study. They may have had hypertension at the time that they were enrolled in the trial, six hours later, or 10 hours later.

This is a very changing disease, and asking that

question when it is a one-time analysis doesn't really mean a lot.

DR. LIPICKY: So, you are saying it was just chance.

DR. EHRENKRANZ: I am not saying it was just chance. I am saying is that it was a real measurement, but the fact is that these are changing kids. The assessment of whether or not a child needs ECMO is not an on/off switch.

In the study I presented, almost 60 percent of the kids were already meeting ECMO criteria at the time they arrived.

So, as they came into the hospital, they were being evaluated; they were being stabilized. They already met ECMO criteria. They were still enrolled in the trial, because they met our enrollment criteria.

In the study that Dr. Straube presented, their OIs were lower, and enrollment in the study. They were not as successful at getting kids in and to that point where they could begin.

We know that the outcomes of these babies are very much related to what they saw before.

DR. LIPICKY: So, let me ask a question. So, you are saying that I should not take the incidence of right and left shunts as any measure of the degree of pulmonary hypertension present in these kids.

DR. EHRENKRANZ: What the application is for or what is the patient population that we are talking about is infants with severe hypoxemic respiratory failure, and most of those infants have evidence of pulmonary hypertension at various times during that disease.

Those may be the babies that respond the best, but they are not the only infants that respond.

One of the potential benefits --

DR. LIPICKY: Your babies responded the worst.

DR. EHRENKRANZ: No, they did not respond the worst. One of the potential benefits of some of the strategies that Dr. Kinsella and Dr. Abman and Dr. Clark have postulated are other ways of our treating these infants that may help our therapy.

Dr. Packer: If I could be rude, Dr. Wessel has three more slides and spent a fair amount of time in their preparation to keep us on the data. I would like to at least finish the presentation of the data.

DR. PACKER: I think it is a wonderful idea to go forward. Let me simply say to remember the purpose here is not to reach any conclusions about approval or disapproval.

Therefore, let me emphasize, combined analyses here are going to be viewed with a great deal of concern because the committee has not specifically gone through the trials or made comments as to whether open label trials

should be mixed together with trials that are double blind, and the individual integrity.

I would ask you specifically not to go over any data on combined analyses.

DR. EHRENKRANZ: I think the trials that are in the analysis are appropriate trials in the analysis.

DR. RODEN: I would be interested in seeing it.

DR. PACKER: Three slides.

DR. RODEN: I have a question, and maybe Dr. Goldsmith would be the best person to answer this. The assumption all day long has been that ECMO is proven effective therapy, and that is based on one British study with 90 to 100 patients.

DR. GOLDSMITH: There are two other studies in the United States, both of which have some question about their randomization.

DR. RODEN: Let me just ask about the randomization specifically, in the British study. The patients who got ECMO went to a tertiary place -- went to the British Massachusetts General Hospital -- and the patients who didn't get ECMO stayed in the Nottingham General Hospital.

Now, it seemed to me that there is a tremendous potential for difference in outcome just based on that.

DR. GOLDSMITH: That question has been raised.

The answer from the British people that we have talked to said that the ventilation therapy and the maximum conventional therapies were comparable in both sets of patients. I share that concern.

There were two studies done in the United States.

DR. PACKER: This could be an entire discussion.

DR. GOLDSMITH: I understand. There are two studies that were done in the United States. They are in your packet. One is by Bartlett in 1986 and one by O'Rourke in 1989. They combine totalled babies who had received ECMO, I think it was 40 patients, in the United States.

The total number of babies now who have received ECMO in the ELSO registry is 14,000, approximately. Is that correct?

DR. PINA: Yes. I don't want to lose a point that Dan had made earlier and sort of to emphasize what Mark has said, in our packet here we have the days to time of ECMO in the INO, the 01 and 02.

Since we are talking about, we don't know the long-term toxicity, we don't know long-term mutagenicity, the patients who had the lower dose were the patients who had the longest time before they had to receive ECMO.

I don't want to lose the dose ranging facts. I don't want to lose that in the discussion.

DR. PACKER: Please proceed.

Agenda Item: Clinical Trials. Trial Summary.

DR. WESSEL: I will just show three slides. I am not going to give a talk. I am not going to talk about meta analysis. I am going to answer a question that was asked me before. What was our committee thinking by suggesting -- in fact directing -- us to stop randomization.

These are the data that they stuck with themselves, in making this decision. This is from 538 patients in the four prospective randomized trials that you heard presented this afternoon.

We see here, if there was no effect on patients who were in the nitric oxide here. The relative risk is 1. However, if the ECMO utilization was reduced in the nitric oxide group -- as it was in the NINOS trial shown here -- and if the 95 percent confidence intervals as shown by the horizontal bars do not cross one, then there is a statistically significant effect of the reduction of ECMO.

The committee that I presented this data to looked at the total number of published studies and our total number of patients, and looked at the relatively risk of going to ECMO, starting with .59, and then looked at the relative risk of ECMO to death.

They saw the same strong trends in all of these even though Dr. Lipicky quite rightly pointed out that our relative risk 95 percent confidence, overall there was a

strong trend to have a reduced relative risk in these patients with .64 with a 95 percent confidence interval at .77.

So, with that in mind, they made their recommendations. In conclusion -- this is the third slide -- for half the children, we believe there is a valuable role of inhaled nitric oxide in their treatment.

Improved oxygenation is undoubtedly of benefit to the child if it can be accomplished with no toxicity. Clearly, further investigation is important, particularly as it pertains to those factors that affect individuals in their response.

We would argue strongly that in 1998 the use of ECMO isn't the appropriate outcome variable to measure the evidence of efficacy of those trials.

We do not believe -- as has been suggested prior to this meeting recently -- that safety issues at this time warrant the withdrawal of all the IMEs for inhaled nitric oxide in the United States. Thank you. Three slides.

DR. PACKER Actually, I think that last point is something that I guess the committee was not very sensitive to.

That is, there is an issue that is related to whether further studies are warranted, or whether they could ethically be carried out, or whether investigator-initiated

INDs should be restricted.

DR. WESSEL: I think it is worth pointing out that an impression that we took away was that one option here today was to withdraw every IND in this country, or any other options.

I think we want to make one very clear-cut plea, that ECMO is the outcome variable and we don't necessarily need to withdraw all INDs in this country, based on safety data that we have seen from European trials.

Agenda Item: Open Discussion.

DR. ST. JOHN: Elaine Fairfield St. John from the University of Alabama at Birmingham. I have conducted a single center trial and have participated with the Ohmeda trial.

I want to emphasize the fact that all these different studies give us different information. It is unfair to try to pin down somebody on the basis of a single trial and say, what would you do.

We need to take advantage of the information that all these trials give us. The Ohmeda trial was done very rigorously so that we could separate out the effects of inhaled nitric oxide from all these other therapies.

That is crucial if we want to look at long-term follow up. We need to know that if babies do poor, if it is because of exposure to a toxic compound.

That type of study, that is very scientifically rigorous, gives us information about biologic effects and about safety issues.

These other trials are equally important, if not moreso, because they are real world trials. This is what we, as physicians, have to face every day.

Now, the question that we have all been dancing around is, if ECMO is an appropriate outcome to be avoided, and using inhaled nitric oxide can save a baby from ECMO, which appears, from all the studies that we have and our experience, does appear to be a life-saving therapy, then we have done you a favor.

That information has to come on three time scales. One time scale is PVV and overt neurologic injury. We can get that information from some of the studies we have now, from one-year data.

Some of the mid-term data of neurologic functioning when it comes to school age is are these children will be impaired in their school performance. If so, is that ultimately going to impair them in their life functioning. Are they going to have other long-term morbidities, in terms of fighting vascular disease or cancer.

All those things are things that cannot be answered except in the tremendous long term. When the FDA

is now under a new mandate to consider treatments for children, if we have to consider all these imponderables over the long term, then nothing will ever get approved for use in children.

I do want to make one comment about the issue that was made about, are we applying a different standard to children's trials as opposed to adult trials.

I would argue that we shouldn't. We should hold them to the same standards. The reason why we tend not to is because it is an emotional issue.

When we tend to start thinking with our hearts instead of our cerebral cortex, then I think we do the children's community a scientific disservice.

DR. PACKER: Let me ask, if you could stand by the microphone for one moment, how many of you are holders of INDs for nitric oxide.

Of those of you who have raised your hands, how many of you, as part of the proposals that you have put forward in order to hold the IND, are giving nitric oxide in a clinic that has a control group, at the moment?

It is a very small number. Let me ask a question. How will we interpret the long-term effects if there is no control?

The question still is, if you find X number of cases of decreasing hearing, X number of cases of difficulty

with motor coordination, X number of cases of cancer, X number of cases of whatever, how will you be able to interpret the data.

How will you know whether all those sequelae are related to either treatment or to the disease for which they were treated or total noise? How will you know?

DR. ST. JOHN: We may never know with some of those issues. In the acute situation where you are faced with, is this treatment going to improve survival or short-term outcome, those are the questions we first have to ask.

The answers to some of those questions can be gained by doing the real world trials where, this is what we would do if we didn't have it at all, and this is what we would do if we have it.

DR. PACKER: But remember, please, real world trials still need to be interpreted. They generate data that still needs to be interpreted. They don't just generate an experience. They need to generate data that can be interpreted.

You have made a plea that real world experiences are valuable. We don't state that they are not. But the reason they are valuable, you are saying to us, is that they generate data.

We agree. The question is, how is that data going to be interpreted if the vast majority of IND holders are

administering this without a control group. What are we using as a basis for comparison.

DR. ST. JOHN: I am not saying that studies don't need to go on. I think with all the things that we don't know about nitric oxide, the studies do need to continue.

We have got a lot of people in here who have a lot of experience and a lot of brain power. I think that we can come up with what it means to evaluate some of the questions that we have with well designed studies.

Obviously, that is not the goal of this meeting, is to design the studies.

DR. ROTHSTEIN: I hope that my words aren't misinterpreted. There do, in fact, have to be two standards.

It is okay to approve a drug for an adult given at age 75, because he may only be interested in an outcome for five years.

On the other hand, with a treated infant, with either a drug or an operative procedure, you may need to be concerned with what the outcome is forty years from now.

Diethylstilbestrol is perhaps the first thing that comes to mind.

On the other hand, we cannot be paralyzed by saying we do not have today 10-year data on a treatment that is just being started.

We also, in thinking about it, have been using nitric oxide donors in infants for many years, nitroprusside. No one has at least hinted or demanded data on mutagenicity of that drug, even though we have been using that for 20 years, 30 years, and we have no evidence whether that is, in fact, an injurious compound over the long term.

DR. PACKER: Nitroprusside, I don't think, is co-administered with oxygen, which is what people are worried about.

PARTICIPANT: It is.

DR. PACKER: Co-administered as a gas with oxygen?

DR. ROTHSTEIN: No, but it is distributed throughout the body.

DR. PACKER: I think it is the difference in the concentration you achieve in the alveoli.

DR. ROTHSTEIN: In the alveoli, yes.

DR. PACKER: Second is, what is nitroprusside approved for in children?

DR. ROTHSTEIN: Let's not get into what is approved for kids.

PARTICIPANT: Let me just mention why we wanted to do this at all. We felt, when the first studies were done, we felt that the design of the studies were not comparable and were not appropriate to the way medicine was being practiced, at least in our institution.

We felt that the way the nitric oxide was going to be given and treatment sort of strategies could possibly be improved upon.

So, we set out to look at the physiology of nitric oxide. We thought we would see what the physiology was. We generated some dose response curves that shed a little light on what was said today.

It is important not just to rush out and do a controlled trial, because this is what happens. The controlled trials were started two or three years ago and now we have a whole lot of scatter of the target and we really can't figure out where the bull's eye is supposed to be.

So, possibly we should do a little bit more physiology and home in on the studies, and then maybe design a trial that would allow for earlier enrollment and allow for the use of nitric oxide with patients failing the trials.

DR. CALIFF: Just a couple of comments about this discussion. I think we have touched on a critical issue that we are going to be seeing more and more, which is how do you deal with the mandate to look at therapies in children.

I think the right questions have been asked. I don't have a whole lot of insight into how to answer them,

except for one potential approach.

We did have 500-some children who have been randomized already who are out there, who potentially could be followed with rigorous follow up measures, to look at these issues.

The second thing I would point out is that if all these IND holders out there actually put their patients onto studies at the same time, it actually wouldn't take three years to get the randomization done and we would get an answer before the underlying clinical practice changes.

I don't really understand the need to have all these INDs out there by individuals who couldn't possibly learn too much of value from these small experiences.

It would seem like there ought to be a better system for getting adequate numbers to actually draw inferences from the studies that are being done.

DR. TEMPLE: Actually, I was going to make the same observation about the number of people who could be followed up. Safety analyses are always meta analyses anyway.

The other thing, if one is going to worry about long-term cancer risks, you probably are not limited to data from the controlled trials.

You probably are potentially interested, at least, in people who did and didn't get nitrates. Nitric oxide was

started out in roughly the same conditions.

The potential of enrolling larger numbers of people in long-term registries is really there. That is the issue.

DR. LIPICKY: I guess that is putting the last question first, and I must confess that that is what the meeting is primarily about.

I must also confess and cleanse my soul, that I feel mildly guilty that we have these INDs knowing that these are baseline clinical trials and have seen the field -- and I will let the cat out of the bag in terms of what I think -- make some very bad judgement on the basis of a single trial that was stopped early and that has a nominal P value published, that hasn't accounted for what was really found and what the right end point should be.

The whole field has jumped on that with a bunch of other things that have much less significance, in one other trial that found absolutely zero.

The field says, we know this stuff works and because people have access to nitric oxide through the INDs, that we did not put on hold, the firm, if it wanted to do more work, could not.

So, the question is, what would the reason be for putting an IND on hold? There is no safety issue. So, if we want to say, you must contribute to science if you want

an IND, you must contribute to mankind if you want to have an IND, how do we tell the people who now hold an IND that they no longer do? Ordinarily we say it is unsafe.

DR. TEMPLE: I don't know the answer but I can tell you what the reg says. Trials that are beyond phase I can -- but rarely are -- placed on hold because they have no possibility of answering the relevant question.

Now, of course you can change the question and perhaps avoid that question. But if we were very concerned about this, I think there is a regulatory handle that would say, it is not in the long-term interest of things to keep doing trials that can't answer the question.

Whether this reaches that level of concern, I think it would be highly debatable, but one could do that with a very strong consensus that this was getting in the way of doing trials.

I should say that there is an additional rule that points out that if open, uncontrolled studies are interfering with the ability to carry out controlled trials that would get a necessary answer, that is an additional basis for putting studies on hold.

That is very clear in the regs and it was done because in some ways the worst outcome is never getting the answer. Then you just keep doing it and you never get the benefit and you don't know if you do or not.

So, there is some potential for that. Whether that is the right answer here, I think, is a much tougher question.

DR. PACKER: Because of time considerations, we will take two more comments, and please try to make a brief question or brief comment and, if necessary, a brief response.

DR. SKEMMING: Jeff Skemming from the University of Florida. I would just like to make a couple of comments regarding where we are going.

I think with regard to inhaled nitric oxide we started out with Dr. Zapol and others showing that we had a change in vascular resistance.

Then subsequent to that focus, it came on oxygenation. I would pose to the audience that I think that there is more physiology that warrants studying.

There are several studies out that now show that in addition to the change in oxygenation, that inhaled nitric oxide can perhaps, inasmuch as it can improve the absorbance of oxygen, that we can improve the elimination of carbon dioxide, and thereby improve the efficiency of breathing and perhaps work with it.

I think that Dr. Abman also posed an interesting concept earlier, that showed that nitric oxide might be working as an anti-oxidant, and that there were

investigations.

I wear a kind of interesting hat because I have a fortunate opportunity, being able to care for both pediatric patients and adult patients in the inhaled nitric oxide studies that are going on at the University of Florida.

I found myself asking, why is it that in the neonatal studies that I am familiar with and were presented here today, that we see such a nice response to inhaled nitric oxide, and we have not seen that in ARDS studies.

I think if we compare the two kinds of studies and the attitudes that people have used to design the trials, I think a very important feature is present there.

One of them is that in all the neonatal studies we have, the investigators are showing oxygenation indices.

I don't know if that is really necessary because all of them are using 100 percent oxygen. They could have just as easily shown some factor derived from the airway pressure and the PAO2.

Now, that doesn't really compare to how the ARDS trials were designed, where they used PAO2 iterations. The thing that really struck me in reviewing all these studies is that I think the inhaled nitric oxide has been used as an adjunctive therapy in the neonatal trials and has been used as a substitute therapy, at least substitute being for oxygen, in some of the adult trials.

I think it is incumbent upon us now -- myself and others -- to investigate whether or not the use of 50 percent oxygen plus nitrogen is less toxic than 100 percent oxygen.

DR. JANECK: With reference to the investigator IND. Mitch Janeck from San Diego.

The way I sort of view the investigative INDs, I think they have been a real bonus. I think the amount of data that has been generated and what we have learned about nitric oxide we just would not have had without the IND program.

Numerous publications have come out describing potential applications for this agent. There is no way we would have had this data without investigator INDs.

I think that is a great stepping off point for determining what areas need rigorous controlled studies. I don't think it is a substitution for it, but it is just the first step.

We can talk about pulmonary hypertension, but we have extensive experience, as I am sure many of you do, giving acute NO for vasodilator testing for pulmonary hypertension.

It is now published and well known that it correlates very well with vasoreactivity. We would not have been able to do that necessarily without this investigator

IND.

You can go down the list of data we have that we would not have had.

DR. PACKER: Thank you. We will move on to the questions.

PARTICIPANT: Mr. Chairman, forgive me for being rude, but there is one safety issue that hasn't been discussed that directly relates to the INDs.

We have studied this in a randomized controlled fashion and I think it is important to just give me one or two minutes.

I think the panel should be aware that in the field of neonatology we have a very positive experience with inhaled nitric oxide.

It is known that there is a hidden mortality during the transport period. One of the demographics that was discussed here was that patients were not accepted into the Ohmeda trial because of surfactant and high frequency.

In fact, as part of that trial, I know that is only a percentage of the problem. When we asked the investigators what was going on, it was not only that, but it was a failure to transfer patients because of economic reasons.

Now, if you add nitric oxide to therapy, to places that don't have ready availability to ECMO or are not ECMO

centers themselves, you are asking for trouble.

Especially if there is a synergistic effect of surfactant and high frequency plus nitric oxide, as part of the Ohmeda nitric oxide study, there was a second phase of our study that involved the withdrawal of inhaled nitric oxide.

In a word, what we found was that for treatment successes there was a nice dose response from 16 to one part per million of nitric oxide on withdrawal and you can just counteract that with changes in the ventilator.

However, if you are a treatment failure -- remember, not all babies respond to treatment -- and you have an oxygenation index, whether you are in the placebo or the nitric oxide group, at around 30 or 35 oxygenation index, you stop the treatment gas. The placebo stays the same and the nitric oxide group the OI goes up to 45 percent.

So, I think that there is a potential safety concern. There was one serious adverse event in the Ohmeda trial that was reported to the FDA, a possible serious adverse event from the withdrawal.

I think that the panelists, not being neonatologists, need to know about that part of it.

DR. PACKER: If you can stay at the microphone for a moment, if I understand what you are saying -- because I

think you may have answered that we have seen a similar phenomenon in cardiovascular disorders, that what you are describing is not a rebound because a rebound is usually seen in patients that are responders.

What you are suggesting is that part of the reason that some babies are non-responders is, although they may be getting a direct benefit from the agent, they are also getting a toxic effect from the agent.

Upon its withdrawal, the benefit disappears and the toxic effect reappears compared with babies that get placebo. Is that it?

DR. JANECK: I don't interpret it that way. Based on the results of all the trials showing absolutely no toxicity, based on ventilator, based on oxygen PVV. So, I would interpret it that way.

What you are dealing with here is, you are starting nitric oxide and you are looking to see if it works.

You may get an acute change in oxygenation but that doesn't guarantee that you are going to be getting away with ECMO.

You continue the baby on nitric oxide and other therapies, and in 24 to 48 hours, the pathophysiology of the baby's disease that underlies it -- whether it is chemical pneumonitis or sepsis and all the things that occur there,

or just aberrant trauma -- has changed the situation.

The nitric oxide is still having an effect on pulmonary vascular tone, but now you withdraw it and you have a much sicker baby and you could potentially get into problems. So, we have that data.

DR. PACKER: Is that alternative explanation that I just suggested possible, given the fact that we have been a little disappointed that the long-term effects are so similar?

DR. JANECK: We didn't see any increased duration on ECMO for treatment failures or their days on oxygen.

DR. PACKER: Why don't we proceed. There is no primary reviewer for each of these questions. Hopefully each of these questions will be very rapid.

What I will ask the committee to do is, for each member of the committee, depending on where they sit, to take these questions on as being the primary responder.

Marv, what I will do is ask you first and then see if the committee has any comments.

In what patient population does inhaled nitric oxide unequivocally decrease pulmonary vascular resistance. What do the time course and dose response relationships look like. Again, I think we can do this very quickly.

DR. KONSTAM: I guess the most striking evidence is in the population with persistent pulmonary hypertension.

I don't think the company -- I don't think the dose response is clear, from the data we have seen.

DR. PACKER: So, the time course is rapid?

DR. KONSTAM: The time course is rapid, but I don't think we have seen data today that make the dose response clear; let's put it that way.

DR. PACKER: Are there any patient populations that you think does not show a decrease in pulmonary vascular resistance?

DR. KONSTAM: I haven't seen enough data about a lot of other populations, including the ARDS population.

DR. ROTHSTEIN: There are many different populations that will respond. It is unclear how to predict which in that group will respond.

DR. PACKER: Does anybody have anything to add?

DR. CROSS: Yes. I would say that a lot of the non-ARDS pulmonary hypertension will respond. Are you talking about primary pulmonary hypertension or some of the post-surgical ones? In our booklet we had about 10 cases, the transplant that we heard, et cetera.

So, I think there are a pot pourri of other groups that respond. I think the big one that is the question mark is probably the one that is developed with a lot of inflammatory activation, ARDSs, where it may be quite complex.

DR. PACKER: We are talking about response here as a decrease in pulmonary vascular resistance. We are not talking about oxygenation. We are not talking about clinical outcomes.

DR. CROSS: Right, and I would say almost all the other pulmonary hypertensions, certainly the reactive pulmonary hypertensions, the primary pulmonary hypertensions.

DR. SESSLER: I think this is a question that points out the value of individual studies. I don't think we know what all is out there.

DR. PACKER: Okay, number two. Neonates with hypoxic respiratory failure, does inhaled nitric oxide unequivocally improve systemic oxygenation?

Joanne, we will ask you to take that. If so, what do the time course and dose response relationships look like.

DR. LINDENFELD: I think the answer is that it does but not for everyone. I think it does appear that there is a dose response, but again, it is not entirely clear.

DR. PACKER: Any other comments?

PARTICIPANT: I guess the dose response, if it exists, seems to be pretty flat. Does everyone agree with that?

DR. PACKER: Dose response doesn't mean that it exists. Dose response means that you can characterize it.

DR. ROTHSTEIN: In initiation of nitric oxide therapy, we may not have initial response at very low doses. You may have a dose response at 20. Once you get that response, you may be able to back down.

DR. PACKER: Are those responses coming from the most recent data? Can you tell me where this flat dose response information is coming from? What data are you pointing to where it says it is flat.

DR. LINDENFELD: I am sorry; say that again?

DR. LIPICKY: Milton just said somebody's statement is that dose response for nitric oxide is flat. The question I am asking you is, what data leads you and/or Milton to that conclusion. Is it the most recent stuff that was looked at or was it the stuff that was looked at early this morning, and I think it was the third or fourth slide that Dr. Zapol showed.

DR. LINDENFELD: I think the most recent data that we saw suggested that, but one of the previous studies, but I forget which one.

DR. LIPICKY: So, it is the most recent stuff.

DR. LINDENFELD: Yes, but in one study there were responders did not respond to the lower dose.

DR. LIPICKY: So, what range of nitric oxide are

you talking about; five to 80?

DR. LINDENFELD: I think the one study did go up to 80.

DR. LIPICKY: Right, and what Dr. Zapol showed this morning was that even 50 for nitric oxide was an order of magnitude lower than that.

I think it would be inappropriate to leave the notion that the dose response is flat.

DR. THADANI: There was a dose response curve in the one slide.

DR. LIPICKY: Yes, for everything from five up. Even 50 is lower than that.

DR. PACKER: Ray, I don't think there is a conflict in what was said in the Ohmeda 01 and 02 trials. Five and up seemed to be about the same.

DR. LIPICKY: Right, because 80-50 is an order of magnitude lower. So, it is at the top of the dose response and it doesn't make the relationship between nitric oxide and oxygenation flat. It just says they are referring to concentrations that are beyond the maximum.

DR. GRINES: (Comment off microphone.)

DR. PACKER: What Cindy is pointing out is that, I guess in the medical review, page 123, from the Ohmeda 01/02 study, there did seem to be a relationship between dose response.

It is interesting. I think that the data that we saw today, for some reason, doesn't actually look like that. That is PO2 as opposed to oxygenation.

Is an effect on pulmonary vascular resistance or systemic oxygenation predictive of clinical outcome; number four. Oh, I have skipped one. Does inhaled nitric oxide unequivocally improve systemic oxygenation and, if so, what is the dose response relationship.

DR. THADANI: I think the data on that was less clear as opposed to the neonatal. There is some suggestion that there is improvement in oxygenation, but I did not see that it was clear that there was much response.

DR. PACKER: I guess I am a little bit confused. I thought we actually saw data in adults with respiratory distress that showed a pretty clear increase.

DR. SESSLER: Then deal with responders and non-responders.

DR. PACKER: There are responders and non-responders in every one of these diseases. Is the response in adult respiratory failure and attendant oxygenational materially different?

DR. THADANI: You can't just throw away the non-responders.

DR. SESSLER: I think one comment that also addresses the gentleman from Florida's comment, he has adult

patients and neonates, both. He was surprised at both the adult and infant response.

DR. CROSS: I think the other difference in physiology that is important in the adults is the degree of inflammatory activation is very variable. There is a great difference between where you are looking at the disease. I think we had that mentioned this morning.

I think this probably compares to the average data, because we have got sepsis and chemical pneumonitis, et cetera, cytokine activation and pneumoinflammatory things going on, to a lesser degree in the pediatrics, and some of them don't even have any, or very little, of the inflammatory activation.

So, Pete's group looks a little cleaner than the adult ARDS group, because by the time we get them, they are really activated and they are in a different stage of the disease.

I think the data in the adults is a little bit harder to get clean that pediatric groups. I would agree that the adults, yes, they respond but probably not as clear cut and unequivocal as the pediatric group.

DR. PACKER: Okay, let's move on to number four, then. We will move to you. Is an effect on pulmonary vascular resistance or systemic oxygenation predictive of clinical outcome -- two parts, in neonates with hypoxic

respiratory failure, second part, in ARDS.

DR. RODEN: Maybe and I don't think so. Maybe and I don't now. Maybe in neonates, and I don't now in adults. I don't think so.

DR. THADANI: I don't think we have seen really data which show that we are seeing a response to oxygenation and outcome. That outcome is not different than with ECMO in some trials, and in other trials with different outcomes.

I have not seen any convincing data that convinced me -- you can forget whether or not it is doing it.

DR. LIPICKY: The questions were worded so that maybe would be a very good answer. It didn't ask you to explain why.

DR. LINDENFELD: If we use ECMO as a clinical outcome, which you discussed earlier, I think I would say probably, for me.

DR. PACKER: Let's be a little careful here. The word predictive is a little tricky. I want to make sure that we are interpreting this question in the way the agency intended to write it.

Are we to assume that the word predictive is equivalent to the word correlative, or is the word predictive --

DR. LIPICKY: I suppose that the way in which that word was intended in the question was that pulmonary

pressure goes down and systemic oxygenation goes up. Does that make the treatment approvable because it predicts clinical outcome.

I think you have already answered these questions in your previous discussion saying that you want to see clinical outcomes.

It would be really easy to go through these questions saying yes, yes, no, no.

DR. PACKER: Yes and no. I think what we have said, what this committee has said today is, if this question is intended to be answered not in a correlative way, but to suggest that a change in systemic vascular resistance or a change in systemic oxygenation is linked to clinical outcome in such a way that they can be used as surrogates, if that is the nature of the question, then I think what we have heard everyone say, including all the presenters and all the consultants, is no.

DR. LIPICKY: I don't know where to go with this question. I think it is very complicated, obviously. If we go down the road of saying that use of ECMO or need for ECMO is an outcome, then I don't think there could be any doubt that the use of systemic oxygen predicts the use of ECMO.

This is the sort of issue that you get into when you have, as an outcome indicator, something that the clinician does.

I think that there might be an analogy here related to hospitalization for heart failure. You know, hospitalization for heart failure is probably predicted by, I don't know, weight gain or pulmonary edema or all sorts of things.

I don't know where we go with this. We are going to have to come to grips with whether or not we accept the clinicians' judgement that ECMO ought to be used as an outcome indicator that is useful in assessing this treatment.

If it is, then systemic oxygenation sure does influence that.

DR. KONSTAM: Marv, we are going much too far on this. It is a very simple question. The question here is, are changes -- as now modified by Ray -- the question is, are changes in pulmonary vascular resistance, or changes in systemic oxygenation per se, is their connection with clinical outcomes so tight that they could be used as the basis for approval per se? That is the question.

I think what we heard from everyone today is no.

DR. LIPICKY: Now it sounds like everybody is changing their minds.

DR. THADANI: I don't think anyone is.

DR. LIPICKY: Then the answer is no.

DR. PACKER: We are going to go on.

DR. CROSS: I think it would be an argument among some of us that we might still be on number four.

DR. PACKER: I think as the question has been revised, I don't think we have heard anyone -- the presenters or anyone on the committee -- suggest that they would approve a treatment for neonates with hypoxic respiratory failure based on the ability to decrease pulmonary vascular systems or increase systemic oxygenation because, in fact, the primary end point of the trial was not either of these variables.

DR. CROSS: The primary reason for getting on the membrane oxygenator is the oxygenation.

DR. PACKER: That is a different issue.

DR. CROSS: I can't separate them.

DR. PACKER: Yes, you can separate them. If you didn't have any data on the need for ECMO, would it be enough. That is the question. Everybody says no, and that is the reason everybody is collecting data on ECMO, which a lot of people think is a reasonable end point.

Okay, next question. Will the data presented today support the use of ECMO as a treatment for neonates with hypoxic respiratory failure? This has nothing to do with INO.

DR. GRINES: It seems that based on the one British study that ECMO did reduce mortality. It seems like

it was also applied to very high risk patients. To my recollection, the mortality rate in the control rate was more than 50 percent and in all the patients that we have seen in these nitric oxide trials, they don't seem to be quite as sick.

My answer to 5.1, I would say, in general would be yes. With regard to 5.2, what are the characteristics of candidates for ECMO? I am still not clear whether we have adequately addressed that.

It seems that the patients who are referred are resistant to other treatments, but it would appear that there wasn't great agreement among investigators as to exactly what kinds of patients would be consistently treated.

DR. ROTHSTEIN: Failure of conventional medical therapies. That is going to be interpreted in different ways by different people.

DR. THADANI: As far as the indications for ECMO, I am still a little confused. Even thought we heard in the trial that some 50 to 60 percent met the criteria and others didn't, I didn't hear anybody define it A,B,C,D,E, and this is the point you have to go with.

I realize that people are trying other treatments, and once that fails, I don't know what that failure is. Is it oxygen index, or the patient just looks bad or what have

you.

I think the disease fatality is so high without ECMO, that it would be nice to outline 1,2,3,4, this is a must. I realize it is a medical procedure. But I think there must be criteria.

We haven't heard anything about it, because if you believe the criteria were there to start with, those patients were denied it initially and then some patients did and then some others did not and some others went on into it.

DR. EHRENKRANZ: If I can shed a little light maybe on that confusion, the one slide that Dr. Clark showed, that implied that only 50 percent or so of the patients transferred for ECMO received ECMO, the difference there is that they were being transferred from a non-ECMO center to an ECMO center.

Most centers who do that cannot wait for the patient to actually meet ECMO criteria. They have a pre-criteria.

They are going to transfer them to try to do that in a safe fashion. Once a baby gets to an ECMO center, then they are evaluated by that center's criteria.

They may have changed en route. They may no longer meet the criteria. That is what that slide was suggesting.

DR. THADANI: But none of the trials suggested that the criteria -- nobody showed how many did not meet the criteria when they arrived.

DR. EHRENKRANZ: Most of our experience, which is not part of the NO trial, is that about 50 percent of babies that are transferred to ECMO are actually placed on ECMO.

In other words, it is a safety feature, and if we have to transfer a sick baby, we have to try to do it in a timely fashion so that they don't die en route, and so that they would not delay what may be a life saving treatment.

In the NINOS trial, 80 percent of the babies who were enrolled in a trial were transferred from elsewhere, got to the center, and we have to first enroll them in the trial. That is part of why they were so sick by the time they were enrolled.

DR. PACKER: Let's move on to number six. Characterize the effects of inhaled nitric oxide on mortality, both in neonates and ARDS and in both cases please answer the question, do mortality data make it unethical, and is it looking at mortality data alone that makes it unethical to perform other studies.

DR. GRABOYS: Let me just make a quick editorial comment. If this group were asked -- this group out in the audience -- were asked to discuss the management of cardiotetic shock or recurrent BTPF or who to send out for

interventional cardiovascular disorders, and we as a group were asked to sit in the audience, and you were sitting up here, with very little experience in that area, then we would be snickering at you the way you, in fact, are legitimately snickering at us.

You have the clinical expertise, as clinicians taking care of critically ill babies and critically ill adults with ARDS.

We don't have that experience. So, from my point of view, as I have listened to the last eight hours, I think it is very important that we listen to you and listen to your expertise.

That has to affect the way we are going to make decisions about clinical judgements, because you have a clinical judgement in these situations that we don't have.

I mean, in terms of enrolling babies, 85 percent of whom will have to be moved from one facility to another, and the complexity of that, I think that is akin to our trying to enroll patients at 2:00 in the morning with cardiotetic shock or recurrent BTBV, critically ill folks. We have to take that into consideration. It is not like entering patients into a cardiovascular protocol in which they are sick, but not as sick as the kind of kids you are seeing.

As far as characterizing the effect of INO on

mortality, I am persuaded. What I am persuaded about is the decrease in the referrals to ECMO and trying to separate those two.

DR. PACKER: Tom the question is specifically designed to focus on mortality only, and whether the effect on mortality makes it unethical to perform further studies.

As you know, these questions are arranged in a sequence to allow clarity about presentation and thinking.

DR. GRABOYS: I am not persuaded that there is sufficient data to make comments about mortality, and I don't think it has had a significant effect on mortality.

DR. PACKER: Therefore, if one bases it on mortality alone, it is unethical to perform further studies?

DR. GRABOYS: No, I don't think it is unethical to perform other studies.

DR. PACKER: Does anyone disagree?

DR. THADANI: No, as a matter of fact, in those summary slides we saw, the mortality was done separately.

DR. GRABOYS: And I think as far as ARDS is concerned, that is at least an area that we have all had some experience with.

These folks who are desperately ill and have terribly high mortality, I am persuaded that INO has a role adjunctively.

Again, I don't think that the mortality data makes

it unethical to perform further studies in that area.

DR. PACKER: Okay, I think from this point onward, the questions get a little bit more interesting. Number seven, in each of the three randomized trials of neonates, with hypoxic respiratory failure, what evidence was there in favor of a benefit of treatment and that is a stand alone question.

We will follow through with 7.1, did these trials find evidence of the same benefit or were these trials otherwise supportive of one another.

7.2, based on your view of the collected data from these trials, is the evidence for benefits so poor as to discourage further study, or so strong that a regulatory decision regarding inhaled nitric oxide might now be possible.

Let me just emphasize, the intent here is very, very different than the question about whether an agent should be approved, which is the conventional equivalent to this question, if this were a different kind of committee meeting.

This is to not actually make any recommendations in this regard. It is really to exclude the two extreme possibilities; that things are so discouraging that one shouldn't try to go further, or things are so overwhelmingly persuasive, that no one should dare to go further because it

is unethical.

Two extremes are represented here, not the subtleties.

DR. PINA: First of all, the NINOS trials has the compliance end point of death and ECMO, and it was a positive trial, in that sense. But if you look at it, most of it was the patients not having to have ECMO.

The second trial, we have initially an end point of oxygenation and I think definitively it shows that it approves oxygenation with the 80 ppm.

Then they added the other end point of the delay in ECMO. So, in some sense, that is what supports the first trial.

Then in the third trial, even though it was stopped early because of recruitment issues, it also supports the delay in ECMO.

I think we keep coming back to the end point of the use of ECMO as the pivotal modality, whether you want to combine it with mortality or not.

Mortality, alone, has not been shown, as we have already talked about. So, I think the trials are supportive of each other. I don't think any one of them is pivotal enough to stand on its own.

I think the data is encouraging for further studies, but I don't think it is so definitive that we can

seem to find it consistently, but if you put the whole thing together it is like a trial of .05 or something like that.

Then you might be perfectly happy with the end point of ECMO, but nevertheless say, look, it is just not convincingly enough demonstrated as a reduced end point. I think the committee should separate those two possibilities.

DR. PACKER: Bob, while you are at the microphone, let me just say that one of the things this committee did not do today, because we were essentially advised not to, primarily because I think, one, there is no NDA and, two, this committee meeting was not constructed for this purpose.

But we did not spend any time going over the integrity of the trials that formed the data base. Now, that is fairly important.

Marv mentioned before the six-to-one difference in the treatment assignments, with the remarkable finding that six patients got ECMO. We haven't spent any time doing that.

PARTICIPANT: What you say is certainly correct. Perhaps in view of all of that, it is unfortunate that we put this question to the committee.

DR. LIPICKY: This question is perfectly fine. You are bringing up the in between. It is so self evident that it works, that no moron would not say it is true. Not after 12 hours of discussion.

PARTICIPANT: That is fine. Then what you bring us, Ray, is that the intended interpretation of the discussion was both that nitric oxide had been shown to change an end point definitively, so much so that no further trials with respect to that end point should ever be undertaken, and that that might be a sufficient end point to act on.

What the committee has said is, well, one of those two things or both are not true and we should not ask which is not true because of the nature of the meeting; is that fair?

DR. TEMPLE: I think Marv's suggestion is that ECMO could be an end point and the status could be supportive and one might consider looking at it; not that it is definitive, but that is possible. At that point, you would look into the flaws of the studies and all those other things.

DR. PACKER: I don't think it would be useful to have the committee deliberate on this any further. I think the issue is that we just don't know what the data are in these studies, because we didn't go through a process -- by the way, very frequently the FDA has proposed that its reviewer do an enormous amount of work, and they are never recognized for this work.

I think it would be fair to say that this review

by the medical statistical reviewer was really, really thorough.

I think this was really, amongst many of the reviews that we get, this was a pretty detailed job. The problem is, that wasn't what our mission was today.

So, we are a little bit ill equipped to be able to carry this question forward. I guess what everyone is saying is that this is not a slam dunk. This is not self evident.

There might be something here and if someone looked at it again with a critical eye, one might be able to reach a conclusion.

DR. LIPICKY: Right, and the only thing I guess I want to be sure that I understand, because what you are now saying is important, is that you did, indeed, look at the data and got the data presented to you that has led other groups to decide that it is moral and unethical to continue trials.

So, you are differing with that opinion very clearly. I want you to be sure that you know that, and that you are not being led down that alley kind of blindly.

DR. PACKER: I don't think that I hear anyone suggesting they believe that the data are definitive. I think there are enough questions about individual trials and about the data of which trials should be used together and

which should not be included in that, and some of the conflicting findings among studies, that suggest the possibility that there might be something here, but also suggests the possibility that there is nothing here that is a critical mass for approval.

I guess the only way to know that is for someone to actually take the question and for people to look at it in our usual fashion.

I don't think we can prejudge that process. Therefore, we do not share this sense that this is a slam dunk and self evident. I don't think I have heard anyone -- unless someone wants to disagree with that summary statement now -- disagree.

DR. THADANI: Perhaps one thing would be to define which patients require --

DR. PACKER: That is just part of the process of putting it all together. I guess that process could only go forward if there were an NDA.

It isn't possible for us to know what a review of such an NDA would lead to in terms of a regulatory decision at the present time because we just haven't done that kind of due diligence. Is that fair?

DR. LIPICKY: Fair.

DR. PACKER: Number eight. I do think that eight, I guess, suggests that we answer a question in seven that

was not actually asked.

That is, would anyone disagree with the statement that further study of NO is indicated in neonates with hypoxic respiratory failure because that next question assumes that it is indicated.

We actually did not answer that question because it actually wasn't specifically asked. So, let me just look around the committee and the consultants and say, the way that that question was answered -- the way Ileana answered that question -- was to suggest that further study of INO is indicated. Does anyone disagree with that?

DR. SESSLER: This is for neonatal hypoxic respiratory failure?

DR. PACKER: Yes.

DR. SESSLER: I think further study is indicated in the way of collecting survey data and registry type of data and further analyzing the data we have. I don't think we want to launch into a huge randomized clinical trial at this point. I think we need to look closely at the information we have.

DR. PACKER: That actually is, without -- I am sorry, Ileana?

DR. PINA: I don't think you can do that at this point yet. I have dose ranging questions. We have toxicity questions that are still raised.

I think that not necessarily a placebo-controlled trial, but I think we still need studies. I am not sure that we have homed in on what dose.

We know 80 is an extreme. We have seen some data that five maybe is better than 20. We keep coming back to the toxicity and long-term effects. I don't think it is that easy.

DR. PACKER: I might as well ask the question that Ray really wants us to answer which is that during the course of this afternoon's presentations, the statement was made that placebo controlled trials of this therapy are unethical and then there was a dissenting view, which remarked on the fact that there are two on-going placebo controlled trials -- I hope I am stating this correctly -- with this therapy.

Those who are participating in those placebo-controlled trials must have concluded that placebo-controlled trials are not unethical.

What does this committee think about that position? That helps to guide the agency in their further discussions. Is that right, Ray?

DR. LIPICKY: Yes, but it may be too much to take on in the time left. We certainly need to know that.

All question eight really asked, the anticipation was that even if you thought it was a slam dunk, that there

was a need for more information.

You said it wasn't a slam dunk, so maybe you need some controlled trials. Maybe that is a question that should have been asked. The question is, if there is more information needed, what are the things that one ought to pay attention to in the design of either the questions or the trials.

That is what question eight was about. So, you are remarking on something that you might not be able to settle in the next 30 minutes. Clearly, we would like to know whether randomized controlled clinical trials are unethical.

DR. TEMPLE: Let's simplify and say, if further trials are necessary. The previous answer said that let's proceed to look at the available data. There might be something there that would satisfy everybody.

Just for the moment say, if further trials are needed, what end points are relevant.

DR. LIPICKY: That is right.

DR. PINA: You just talked about the beautiful review that the FDA has done on the subject. I guess something was brought to my attention that I didn't realize.

This field has evolved so much in the last few years that there probably have been improvements in the care of these infants.

We have heard about the treatments, we have heard about osculatory ventilation and surfactant. I think whatever study gets done needs to be done with the state of the art today, which may be surfactant and osculatory ventilation, and not exclude them, number one.

Number two, there is enough discrepancy in severity of the infants disease state at the time of entry that that may be the source of a lot of discrepancy.

I think some sort of uniform definition if it is possible -- if it is not possible because it is such a complex field, it may be that uniformity and severity by critical scores -- and we come back to scores again -- should be done and should be added in a trial, to try to make it as uniform as possible, so that we are not comparing apples and oranges.

DR. PACKER: Ileana, you have answered question number 8.2 inadvertently. I will seize the opportunity of your having taken that initiative.

I think what you are saying is -- I don't think it is inappropriate to ask 8.2 at this time. You are suggesting that the content of controlling for these factors, in fact, you would encourage that treatment be evaluated on top of these factors because they represent best available therapy.

Therefore, how the sponsor deals with that, it

could be by stratification. It could be by factorial design. One thing you would disagree with is by exclusion. Is that fair?

DR. PINA: That is fine.

DR. PACKER: Would anyone disagree with that?

DR. TEMPLE: You might not do either of those things. You might not require them; you might not stratify them. You might just let them fall where they are and analyze them by covariants.

DR. PACKER: But the one thing that we are saying is that one shouldn't deal with it by exclusion. Thanks, Ileana.

DR. KONSTAM: I would just like to add to that. I think Ileana said it, but also in terms of the underlying condition, there was a good case made that there is a likelihood of a diversity of response based on the underlying condition.

So, that is something that really has to be looked at carefully, as well as concombinant treatment.

DR. CROSS: Could I ask the group of cardiologists. If you have got a newborn kid. If there is a right to left shunt, there is pulmonary hypertension, they are toxic, what drug do you want used other than NO to lower the pulmonary pressure and decrease the shunt.

DR. PACKER: That is not the question.

DR. CROSS: Okay. My word is that it is already state of the art in neonatology units everyplace to use NO, and I would suspect that if we all asked ourselves that if we had a kid who got ready to get hooked up to the membrane pump who fit some of the classification bits that we saw today, whether we wouldn't want NO tried in our offspring.

So, the real question is, something has moved very close to state of the art and we have dragged behind on the approval process, and we may continue to drag behind.

DR. PACKER: Let me emphasize what I emphasized before. The question that you are posing is not the question that is being asked of us.

It would be very easy to answer that question -- if not easy in the point of view of the committee -- if the only hat we were wearing was the hat of the physician.

I think that the question that is being asked of us is what are the data, what do the data tell us and how persuasive are they.

That is the only questions that are being asked of us. Nobody is asking us what we would do in the privacy of our clinics or hospitals.

If that were the question being asked, all one would have to do is take a democratic poll of doctors who take it, and just ask those who are in the audience who likes NO. If the majority of people said yes, then they

would approve it. So, that is not the problem.

DR. LIPICKY: There is something important, I guess. What do you see as dragging on the approval process. If we had an NDA, we could be deciding whether it should be approved or not.

DR. CROSS: I am being the devil's advocate.

DR. LIPICKY: No, but the approval process, what is holding it up. As I heard many saying, the thing that is holding it up is an adequate clinical trial data base.

So, it isn't the approval process that is a problem here. The problem is there is not a good enough controlled clinical trial data base to show it on the screen and having people come to the conclusion, that I am convinced.

They might come to a conclusion after they argue about it for 12 hours. That is the problem.

DR. PACKER: I think it is hard for the FDA to do anything unless someone makes a request. There is no NDA.

DR. CROSS: I do point out that NO, our bodies make it, our noses have .2 parts per million of it. We are breathing it all the time.

We make more NO in our bodies than the NO that we deliver to the babies. There are now nitrate-free diets showing how much NO the body makes every day.

I have this mixed feelings on toxicities of too

much. But too much salt, too much melatonin, et cetera, et cetera, will be toxic.

It is a very excellent vasodilator and we are all using it for vasodilation. That is the frustration of the process.

DR. LIPICKY: Provide us with an NDA.

DR. PACKER: As the people who support the lottery would say, you have to play to win. Okay, question 8.1. What should be the primary end point of the subsequent study.

NINOS utilized death or ECMO. Studies 01 and 02 utilized the combined end point of death, ECMO, abnormal neurological sequelae -- I guess just normal neurological sequelae; I don't know what an abnormal neurological sequelae is -- and bronchopulmonary dysplasia.

Do we believe that these are the most appropriate end points for further study and is mortality alone an appropriate end point?

I guess just to facilitate things, I guess I haven't taken a question and I will just run with this. I think these are reasonable end points. I think the committee has said these are reasonable end points.

I must say, I have a personal preference for more comprehensive end points, so I happen to like that ECMO, neurological sequelae and bronchopulmonary dysplasia,

because I think it includes outcomes which are clinically important.

Having three out of four outcomes which are clinical important, it is more comforting to me than only having one of two.

I think mortality alone is inappropriate. It is not an accurate measure of outcome here. It is not comprehensive.

The treatment strategies which are utilized by physicians equalize the playing field. It is possible that physicians would not let the differences in mortality converge from a clinical trial. I will ask the committee if they disagree.

DR. CROSS: I don't disagree with what you mentioned. If you are worried about nitration or oxidation phenomena reacting with NO and making pyroxinitrite or whatever, the autopsy specimens there have been on NO could deal with that for nitrate approaches.

DR. PACKER: Did you have a comment?

DR. TEMPLE: I was a little curious. If someone were able to study mortality and show benefit, including all that other stuff, that would be cool.

DR. PACKER: That would be fine.

DR. THADANI: ECMO, we were saying, is a mortality improvement, ECMO alone. If we could show that, that would

be good on top of ECMO or whatever.

DR. LIPICKY: Mortality would be good any time, but if you look at what this is competing with, it is competing with ECMO.

I think with ECMO you have got a 96 percent survival. So, it really is a question is, if you want that mortality, that is fine. It is just, would that be reasonable for anyone to bet their cookies on.

DR. THADANI: Then perhaps what you might want to do is show that like ECMO, it reduces mortality.

DR. PACKER: I don't think he said that. I think Bob's only point was that the question was specifically asked, would mortality alone be an appropriate end point.

The committee does not intend to suggest that it is not an appropriate end point. If one could achieve it, it would be a wonderfully appropriate end point. It just shouldn't be required as an end point for approval.

Now, all the issues that we have just talked about in neonates with hypoxic respiratory failure are now brought up in adults with ARDS.

So, the questions are identical. We should be able to go through these very quickly.

MR. KONSTAM: I think it is about a month since we looked at the ARDS data, but I really don't recall anything that supported any benefit on outcomes, based on the data

that we saw.

So, I mean, I would just say in response -- that is basically my response to 9.1. 9.2, I would say that I think that there is reason to go forward and conduct additional trials and let's get to what the end points are.

I think that we agreed that ARDS is a more complex, dirty, if you will, condition than it seems to be looking at it in neonates. That work should be conducted.

DR. PACKER: Marv, the actual issue of end point is question 10. Let's just ask if anyone on the committee disagrees with what Marv has concluded, which is that the present evidence doesn't really indicate a signal, but he would not either rule out such an effect, and therefore believes that further study is indicated, should not be discouraged, and certainly things are not a slam dunk.

DR. KONSTAM: I just throw in another physiologic editorial comment. My own guess is that the difference is more than just that ARDS is dirty.

I interpret the data set as being highly supportive of the benefits of neonates being mediated by a change in some kind of PDA.

So, it is really a very specific oxygenation effect that you can get as a result of pulmonary vasodilation.

I have reason to be more skeptical that you are

going to see the same kind of end points in ARDS.

DR. RODEN: Are we on 9 and 10?

DR. PACKER: We are really on nine.

DR. SESSLER: I think the oxygenation data is sound enough to go forward, and that is just about all you can say about it.

There is not an unfavorable trend and there is not any real tremendously worrisome toxicity data. So, certainly it warrants further investigation.

DR. THADANI: Also, there is the difference in outcome in children because the regeneration process might be much faster in kids. I think it is two different diseases, two different processes.

It was interesting to note that the oxygenation was better in almost all the trials, and yet the outcome is not different from ARDS, despite that.

DR. PACKER: Okay, if further work on ARDS were to go forward, in the past the division has supported a principal end point of time alive and off respiratory support up to 120 days.

If further study is indicated in ARDS, is this the most appropriate end point? Remember, the end point presented this morning was, in fact, this end point, time alive and off ventilatory support.

The question is, should the sponsor change what it

is doing, or is this okay for further study and potential regulatory action.

DR. LINDENFELD: As Marv said, it has been a while, but I think this is an appropriate end point for ARDS. We haven't explored all this data in near as much detail, but I think this is a reasonable end point. I think anything shorter term would not be adequate.

DR. PACKER: So, you think the present policy should pretty much stay in place.

DR. LINDENFELD: Right.

DR. SESSLER: One thing about that, I think you need to look at the 120 days as how is this being expressed exactly.

If a patient in the control group, let's say, is on mechanical ventilation for 13 days on average, and INO patients are on it for 11 days, then the question really becomes, do you subtract that out and are we now comparing 107 versus 109 days, and what is the likelihood that that ever reaches statistical significance with 100,000 patients. My question is how you would exactly look at that.

I think duration of ventilation is a reasonable end point to look at, but I think we need to be very careful about definition so that you don't select something just because somebody else did.

DR. KONSTAM: I just want to second that. It is

not crystal clear to me that this is the way to express it. I guess I would agree to the point of saying that some outcome that incorporates survival and getting a patient off a respirator would be the way to go.

It might be time they stay off it and are alive, it might be something other than the way it is stated here.

DR. CROSS: I think there are real problems with the ARDS studies, if you take a page out of any of the other ARDS studies.

There are going to be more problems with NO, because it does interact with the inflammatory mediators, and NO itself is changing, with all the inflammatory mediators at the stage of the disease.

I think if we look in our black books again, there are 15 articles here by surgeons who are giving it post-transplant, even post-liver transplant, post lung transplant, post-heart transplant.

I was at a NATO conference in Greece last year that did ARDS. The surgeons in one case in England, they had them on NO before they left the OR and they left them there for three days.

They swore that this was so good that they were unwilling to consider a controlled trial. So, you are in trouble. I think that we are in trouble. It is already state of the art in Britain.

DR. PACKER: That is no problem.

DR. CROSS: I think in early ARDS when the inflammatory immune part is just starting to shape up is the time when it may do some good, if you really believe that it modulates inflammatory immune reactions.

Once they are flaring away there, throwing in NO doesn't have a scientific basis. The construct is telling us it is very good and in ARDS I think it is something that it is very important to look at.

I think the groups need to be taken apart, if NO studies in global ARDS are going to show anything at all.

DR. PACKER: Let me just emphasize, it is not our problem. It is the sponsor's problem. Our charge is to evaluate data.

DR. LIPICKY: I think the way to look at the question says, if somebody came in and said, I know it is different from placebo based on this end point, this number of days alive off respirator, and it was statistically significant and convincing, would you say, go away, you measured the wrong thing?

DR. CROSS: I probably would. In the surgical group I use A, develop lung infiltrates following surgical operation. That may be the most reasonable end point.

DR. LIPICKY: That is fine. The only response that is being asked is, if someone came in with that data,

would you tell them, go home, I don't even care about that. That is the only question.

You don't have to decide, based on how you think nitric oxide works, and what you think the pathophysiology of the disease is, whether the sponsor would find an effect on that end point. That is not what the question says.

DR. PACKER: Look. Let me just add one thing. I guess I would still like to see some creativity in divising perhaps an end point which is a little bit more comprehensive than this one.

That is only because I think that ARDS is such a complicated disease, only 16 percent of patients die of pulmonary failure.

I guess if someone is going to get approval for ARDS, I understand one can deal with that by looking at efficacy and then safety, but the decision making process would be a little bit easier if some of the outcome measures, which are important indications for physicians, are incorporated into the primary end point.

DR. SESSLER: I mentioned earlier I think the incremental changes in lung dysfunction may be of interest, to look at safety as well as efficacy issues in a fashion that would quantify it.

DR. PINA: I am looking at the time element and I am wondering if 120 days may actually not be enough. A lot

of our centers are developing these ventilator units and patients who are on prolonged intubation are much more rapidly going to trach and getting very, very slowly weaned off ventilators.

They go through rehab and developing their pulmonary valetory muscles. I am wondering if, rather than 120, we should be adding another 30 days and asking for the experience of people who take care of this.

I agree, I would like to see some other like multiple organ failures and renal function deterioration is very often also the exit of these patients that end up going into dialysis and then ending up with sepsis.

DR. SESSLER: I can speak to the long-term effects to a certain extent. There was a registered study of three hospitals in Philadelphia. By the end of three or four months, everybody with the exception of perhaps one or two percent, everybody was either dead on NO.

After 90 days or 120 days there are very that are still remaining on ventilation somewhere, based on a pretty sizeable survey.

DR. CROSS: The global assessment, it sounds crazy, but I think it does incorporate, in the dialysis and the sepsis and the amino glycocyte, et cetera, is the hospital bill.

DR. PACKER: Okay. I think you are quite right.

It does. Maybe we should can capture that in a different way.

DR. SESSLER: Well, we can. Actually, you can capture it a different way. There are test scores and there is also some preliminary evidence from failure scores, that a score on a given day can determine hospital charges and, consequently, capture it all.

DR. PACKER: Okay, last question. Most of the current INDs for INO are for a single center, based on controlled prescriptive studies in adults, children and neonates. Should the division be more restrictive and why.

DR. THADANI: I think those studies don't prove a point, because they are either baseline control or descriptive in nature. They can only prove a hypothesis regarding an efficacy which could be pursued.

Now, how many INDs you give, I don't know. I mean, there are so many hands, if they had all participated in the trial, we would have had the answer right now.

I would encourage to do the control trials, and by now we would not be talking about what we are doing. So, I would have preferred to see controlled trials.

DR. PACKER: So, is your answer that the division should be more restrictive?

DR. THADANI: I personally would think so. If there is already an approved indication and you want to look

at something else for the definition -- but here, we are still talking after eight hours and we don't know how to use the drug, which indications, I think my answer is yes.

DR. PACKER: I think this is sufficiently important that we need to hear every member of the committee comment. Ileana, we will start at the other end now.

The question is, what should the committee's advice to the division be on current INDs for INO. Should they do nothing? Should they be more restrictive?

DR. PINA: That is a tough one. I would think that anyone who gets an IND in an institution has written up a protocol that is investigator driven and has put it through the IRB.

I know that I can't get an IND unless I have an IRB approval or protocol of my own. If people were willing to do that and do a real protocol so they can use the product, then we would have some real data, and people could publish that and they would have small studies, but maybe important with each other. When added together, maybe we would have a body of data.

I am more for restricting. I understand that a lot of the clinicians here are really banking on using this agent as life saving for many of their patients. I think we should just be more convinced of the end point, other than ECMO.

DR. PACKER: Okay, there are two votes for being more restrictive.

DR. GRABOYS: Assuming that everyone based closure on the end points and what we are really trying to ask, then we want to be restrictive. We want to find centers that are going to deal specifically with the issues that are raised, that could be more readily carried out in a restricted, high volume center.

DR. PACKER: So, your answer is yes?

DR. GRABOYS: Yes.

DR. GRINES: I think we should be more restrictive.

DR. RODEN: There is a subtext that we haven't discussed and that is to what extent the sponsor is willing to go forward, at this point, with organizing the required trials.

Assuming that the agency and the sponsor can come to some sort of agreement about what sort of trials ought to be mounted to demonstrate efficacy, then I would strongly favor withdrawing all the current INDs and only allowing pivotal trials to go forward.

Otherwise, you get into the situation where there is a great perception that the drug is safe and effective in certain situations, and no sponsor.

DR. PACKER: Let me, I guess, underscore what Dan

has said. Any vote here is predicated on the fact that the sponsor is willing to pursue further studies.

The major motivation for recommending restriction is to allow these studies to move forward in an expeditious fashion.

Were the sponsor not to go forward, or if no further studies were indicated of a placebo controlled nature because subsequent filing and review resulted in approval, the situation would be very different.

So, the concept is, one, in the circumstances that the sponsor files an NDA, is told close but no cigar, please go out and do more trials, and they are willing to do them, then the advice which is being made right now would apply.

DR. TEMPLE: Let me just shed some light here. We would be doing this in order to get the proper studies done. That would be the reason, not that we hate to have it go on in the absence of good data, which is another possible reason one could study, but because this would be necessary to get the trials done.

DR. PACKER: First of all, we probably need to complete the process of voting.

DR. TEMPLE: But there is a piece of this --

DR. PACKER: I think it is important, but maybe we should make another round.

DR. LINDENFELD: I agree with how you summarized

it. I do think that if the sponsor is going to ask us to look at all this data soon, I do think there is a signal here. I think that is what we are doing and I think that would be a good thing to do. I would hate to see things withdrawn.

PARTICIPANT: Well, the sponsor is going forward with a trial. They have a contract with Duke University to complete a randomized controlled trial.

It is self serving a little bit, because it is our trial, and so I have a conflict of interest, no question. But there is a trial ongoing that is randomizing to placebo, and that outcome is a reduction in the need for ECMO. It will not likely show a difference in effect.

DR. PACKER: Why don't we go through.

DR. CROSS: I have a sort of in between one on this one. I don't think we should end the INDs. I think the FDA and the sponsor should be playing activist roles in pursuing what is right, which is to get the issues clarified.

First, see what all the INDs together and try to get the surgical society. Try to see what is available through orphan drugs and volunteer health organizations that are interested in this problem.

For example, Cystic Fibrosis throws clinical trials together where FDA is sponsoring it, the Cystic

Fibrosis Foundation is sponsoring it and the drug company is sponsoring it.

Try to answer some of the questions and clean up groups of INDs out there who are all studying the same thing, through trying to put government and private industry and maybe even vested volunteer health organizations into the hunt, much the way I think Cystic Fibrosis has done this rather ideally.

DR. PACKER: But your vote on this question is that the division should not be more restrictive?

DR. CROSS: I think they should be activists in doing what is right. I don't think they should all of a sudden put out an edict that we are taking all your INDs; no.

DR. PACKER: I think the presumption is that this is a -- if the agency were to take such an action, it would be taken in a context where there was a constructive plan to go forward.

DR. CROSS: Well, you probably have one company involved and they need a bone and something to start, and they can't organize studies of everything. First, they need to study one thing so they have something they can show.

I don't think the company can afford to do all the clinical studies on all the INDs that are out there on this drug, given the tremendous cost involved.

DR. PACKER: I don't even think that that is even being remotely contemplated, considered or recommended. I think the concept is that if further study is deemed necessary, the sponsor is willing to go forward and carry it out for any indication.

DR. CROSS: I would think they are going to get a very wild thing from the thoracic surgeons and heart surgeons. It would be interesting to see how they organize a study of particularly that group because that is one that is right out there, I am sure, on a number of these INDs.

DR. SESSLER: I would say definitively no. Actually, I am a little surprised that we are so eager to withdraw this, from a couple of perspectives, I think.

One is that if we truly believe this is harmful, then we should withdraw it for that reason.

If it is because we can't launch new trials because there are other individual investigator INDs out there, until we can launch such a trial that is available to all those folks who have their own INDs, there is absolutely no reason to withdraw it.

I think that by having individual INDs you are in fact getting a lot of scientific evidence and information in new areas.

I think the bone marrow transplant area, particularly, is exciting. I think we should really, for no

reason, curtail that flow of knowledge.

I think what we should do is require more of the IND holders. We need to get more safety information and we need to get more long-term follow up.

There is no reason why we can't get more data on the patients who are enrolled in these studies; require that, but not in any way stem the tide of new ideas, new fresh ideas, until we have something that is a good alternative.

DR. PACKER: Marv, I am really saving you for last.

DR. LIPICKY: Let's say we wanted to do what you just said. How would you suggest we do that?

DR. SESSLER: I said a bunch of stuff.

DR. LIPICKY: If we want to get follow up data. So, how would we do that?

DR. SESSLER: I think we need to focus on areas of safety concerns.

DR. LIPICKY: I understand, but how would we do that. You said we could. We have a bunch of INDs out there.

DR. SESSLER: Requiring the investigators to have time follow ups wherever possible.

DR. LIPICKY: What would we do if we didn't get their letters.

DR. CROSS: Refer them to the IRBs, or ask the IRBs, and get them involved, possibly.

DR. LIPICKY: Ask the IRBs?

DR. CROSS: Aren't the IRBs tracking what they are doing?

DR. LIPICKY: So, we would write to the IRBs and say, IRBs, we are trying to get long-term follow up. Would you please tend to our getting those reports?

DR. CROSS: Maybe don't release the IND without a promise to get it, and make that some sort of condition.

DR. LIPICKY: Isn't that being restrictive, which you said don't be?

DR. CROSS: I support you on that. You are being activist in trying to do what is right.

DR. TEMPLE: That is restrictive. I think we are encouraged to make those that part of the protocols, and if people don't send in the reports they are supposed to, we can terminate INDs for that. We don't very often, but we can.

DR. LIPICKY: But you think long-term follow up for uncontrolled trials is useful? All those kids are going to have troubles. So, we are going to blame everything we see on nitric oxide. Every tumor will be produced by nitric oxide. Every neurological problem will be produced by nitric oxide. Every bronchopulmonary dysplasia will be

blamed on nitric oxide. That will be useful to you?

DR. SESSLER: I think some data may be better than no data.

PARTICIPANT: No.

DR. LIPICKY: If you draw a wrong conclusion of what the data will show, nitric oxide is terrible, because every bad thing that happens will be attributable to that. There is no control group.

DR. TEMPLE: Ray, the key recommendation I heard is that if it turns out that somebody is trying to do the right studies and all these INDs out there are messing it up, that is the time to move in.

Until there is something like that, that is being messed up, there wasn't a good case for taking an action.

DR. LIPICKY: That is when we become an activist.

DR. TEMPLE: That is what I thought I heard.

DR. SESSLER: We all have long-term data which I think is important. Safety information.

DR. LIPICKY: No value if it doesn't come from a control trial. You can't interpret it. An open label, just using A strength produces nothing useful; nothing, zero.

DR. PACKER: Your view on the issue of question number 11, should the agency be more restrictive?

DR. ROTHSTEIN: It should be guiding in how the INDs are carried out. I think we need controlled studies. I

think there are also many areas that we haven't touched on today -- bone marrow transplant, coronary pulmonary bypass separate from transplants. There needs to be some typing.

I don't have the answer for Ray about what the stick is, other than if the data is not provided during X period of time, then the IND is withdrawn. Maybe that is the way to go. I don't know.

DR. KONSTAM: I think I would answer two different ways. I would say that the agencies should have been more restrictive in the beginning.

I think that it would be awfully nice if, as a new drug is coming out of the bag, if there is a way to influence industry to conduct trials in such a way that we can get a useful data set, because I don't think this is as good as we could get right now. So, now we are in that situation.

I think there is an important lesson here, in terms of -- I don't think every investigator IND really serves a useful investigative purpose.

I think they are often compassionate use trials because the investigator has a strong bias that the drug has an effect, but I don't know how much good in general we get out of these investigator INDs.

I think there is another point in terms of the current state of affairs, which is that the drug is out

there.

I think you cannot deny the sort of word that we have heard from the community out there using it, and I just want to make the point that if we were sitting here creating a guideline now, instead of talking about regulatory process, we probably would wind up recommending inhaled nitric oxide.

Perhaps we could even call it level A data because there are randomized controlled data. Given sort of that context, what do you do when the drug has already been widely in the hands of the community. There are a lot of people out there who believe the trials that have been done.

There has been no NDA filed, so there has been no formal action by the FDA. I think some of the comments that are being made here, I will paraphrase it differently saying, in that context there would be a real down side if you say, now we can start withdrawing this or being more restrictive. I think that there is that context that has to be viewed.

DR. TEMPLE: I think this conversation has been very useful. It is just worth mentioning that there is a completely different conversation going on in the nation.

There are several bills pending before Congress that would make essentially anything that a physician wants and a patient wants also available, with little capacity for

the FDA to restrict it in any way.

All of that relates to matters of personal freedom and things like that, which is another theme.

Of course, our response to this is that we think it is very important to eventually get the data, and when that kind of access interferes with getting it, it is really a detriment to the whole community.

So, the conversation is quite helpful, but it is some interest that the political process is looking at some aspects of this from a very different aspect at the moment.

DR. LIPICKY: It is a little bit self serving, I suppose, but the history here has some relevance. Marv, I think you are addressing that.

At the time that nitric oxide started out, what we knew of as regulators is that there would be three adequate, well controlled trials performed, that were dose ranging, that were conducted using protocols that we had reviewed and where everybody had talked to one another and everybody had gotten together.

We knew that if the outcome of those trials was favorable, everything would be terrific. The data you are looking at now is that two of the three trials we knew of found absolutely nothing statistically significant.

One of the trials was aborted prematurely, and I think that that is something that can be argued about and

talked about for a long time. The other two trials, nobody ever knew anything about.

Nobody was involved in those protocols. There was very little in the way of prespecified stuff and there is no statistical point of view.

Because of a single trial, a single trial, that got published in a prestigious journal, the field said, we will no longer study nitric oxide.

The other trial that was going on -- two of them -- had to stop and analyze themselves as a single one because they could no longer recruit a patient. If things had gone along okay, everything would be cool.

DR. KONSTAM: Ray, let me just say I did not make my remarks to be critical in hindsight.

DR. LIPICKY: No, I didn't take it as critical. The trouble is that time zero would be new, and then as time evolves you have to make an adjustment.

DR. KONSTAM: I don't know how any of that relates to the granting of individual investigator INDs.

DR. LIPICKY: We reasonably agree with that. We agree with the notion that there has to be a lot of brownian motion, and every once in a while an amoeba breaks through the barrier.

DR. TEMPLE: We generally don't try to restrict people's ability to carry out things of interest to them,

unless there is good reason for it. Very widespread use of something that is dangerous, that would be a reason, use that gets in the way of doing definitive studies.

As Ray has said, we thought the definitive studies were going on. Ordinarily in that case, we would not necessarily try to stop them.

DR. KONSTAM: But you just asked us the question of whether you should be more restrictive.

DR. LIPICKY: You have seen the outcome of the last five years. We are asking you to be critical and say, you did wrong. We are willing to listen to that, and do something different. You almost did that, but now you are backing off.

DR. PACKER: Let me ask Ray an operational question. Nearly everyone on the committee has, in some way, shape or form, suggested that the present situation is not optimal, and that some degree of -- the word restriction may or may not be appropriate -- that some guided approach is what is needed, that the present plethora of uncontrolled experiences does little to foster the knowledge about the drug and does expose cases -- although in a very well-intentioned fashion -- to a drug whose at least long-term toxicity is definitely not -- the long-term stages are definitely not known.

I guess the question I have is, is the division in

a position to make judgements about which INDs should be granted or not?

In other words, in general, can you imagine what it would mean if all 300 IND holders were to say, okay, they want something a lot more scientific than what I submitted before.

I promise that I will behave and I will put something in. And they will put a whole bunch of things in which may or may not meet whatever scientific standards are being proposed.

DR. LIPICKY: I don't know the answer to your question, but we have heard what you have said and we accept what you have said, and we will find out what is going to be going on here, and we will try to determine whether our policy is standing in the way of getting a controlled clinical trial done.

If our policy is standing in the way of getting a controlled clinical trial done, if our policy is standing in the way of getting a controlled clinical trial done, I will try to convince Dr. Temple to allow me to try to figure out what you just said.

Then we will write to somebody and tell them that they are in trouble.

DR. KONSTAM: I would just like to frame this again by saying that there what I would call a legitimate

disconnect between the regulatory approval process and the way the physician community makes it decision, on a fairly formal basis, in fact.

I think that is what we see. If the drug has permeated into the community and the trials go on, you must expect that the community will make those decisions independently.

DR. LIPICKY: Of course, but I am going to exaggerate what I heard you say. What you said is that if you recognize that the community has made a judgement that is impeding the progress of real drug development on the basis of its behavior, exercising regulatory authority to make sure that that doesn't happen -- that is what I heard you say.

DR. KONSTAM: I would say it is a lot easier to do that, if you had started it, proactively.

DR. LIPICKY: I understand. What I also heard you saying is that you think that the medical community has made that distinction.

DR. KONSTAM: No, I am not sure whether it has.

DR. LIPICKY: Then we have no basis for doing anything.

DR. KONSTAM: What I said actually is that, I think if you were writing a guideline today for persistent pulmonary hypertension of the neonate, I think we would want

to recommend inhaled nitric oxide on the basis of level A or B evidence.

What I am saying is that I don't think I would go so far as to say that I think the community has made a mistake.

I think that the level of evidence that exists or has been reviewed is not sufficient to satisfy the appropriate regulatory process. But that is not the same as saying the community has made a mistake.

DR. LIPICKY: What basis do you have for saying we should be more restrictive. You have just taken away everything I had.

DR. TEMPLE: There is a reason, Ray, and we wrote a rule to allow for this. If trials that aren't well controlled studies are interfering with the ability to do the studies to get the answer, we can discontinue the treatment INDs or anything.

DR. LIPICKY: You normally need the answer if you don't know it and Marv says that he knows it and the medical community knows it.

DR. TEMPLE: No, he didn't. He said different people use different standards in different settings. Sometimes you go with half a loaf when you don't know what better to do. That is hardly news.

DR. PACKER: Let me just maybe close this matter

by simply saying that I think that the committee -- I believe unanimously -- supports the concept that the agency, if the development of this drug were to continue, that the agency should take a more disciplined approach to the INDs. Would anyone disagree with that?

DR. THADANI: A disciplined approach?

DR. PACKER: A disciplined approach to INDs.

DR. LIPICKY: Don't even ask if anyone would disagree. Just make the statement.

DR. PACKER: It sounds like that is unanimous, and we are adjourned. Thank you.

[Whereupon, at 6:40 p.m., the meeting was adjourned.]

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84th Meeting
Cardiovascular and Renal
Drugs Advisory Committee

First Day of Proceedings

DATE(s): Thursday, April 9, 1998

COMMENTS: WORD (1) {3,15} = Keyword (number of occurrences) {page,line number}

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