We're scheduled for a 15 minute break, and plan to be back here at 25 after ten. Is my watch correct?

So we'll start again at 25 minutes after ten with the questions and discussion.

(Whereupon, the foregoing matter went off the record at 10:11 a.m. and went back on the record at 10:27 a.m.)

CHAIRPERSON CHESNEY: We are ready to begin the discussion, and I'd like to turn the microphone over to Dr. Victor Raczkowski, who is going to present the questions to us and also maybe provide feedback to us as to whether we can make up our half hour.

DR. RACZKOWSKI: Hello. I'm Dr. Victor Raczkowski. I'm the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products.

And to answer the second question first, in order to allow more time for discussion, I've discussed it with Dr. Murphy and the pediatric team, and we hope to extend this morning's discussion for at least an hour to have adequate time to discuss the

proton pump inhibitor template.

And let me turn now to the questions. We have five questions for the committee, and the first question is: can the efficacy of a proton pump inhibitor for the treatment of pediatric patients less than one year of age be extrapolated from adults? Why or why not?

And as you've heard from our speakers this morning, the pediatric proton pump inhibitor template has taken the position that efficacy cannot be extrapolated from adults to pediatric patients of less than a year of age.

Question number two gets into some of the design issues of the studies, and are the designs of the efficacy studies requested for pediatric patients less than one year of age, that is, randomized, double blind, placebo controlled studies of a treatment withdrawal design acceptable? And if not, please specify the components of the study designs that should be changed, and please suggest an alternate ethically acceptable trial design to establish efficacy and safety.

Then in Questions 3 and 4 we move to two different populations since we anticipate this is where perhaps much or most of the discussion will be. Question 3 deals with neonates and pre-term infant patients asking (a) whether the efficacy endpoints chosen for Study 2 were acceptable, and if not, to please suggest alternative clinically meaningful efficacy endpoints for pathological gastroesophageal reflux in this age group.

(b) asks whether the specified trial design inclusion criteria, monitoring, and assessments are adequate or not, and if not, to please suggest alternative or additional criteria, monitoring, and/or assessments.

Three (c) asks whether the safety endpoints chosen for Studies 1 and 2 are acceptable and if not, please suggest additional safety endpoints.

And then 3(d) asks for both the neonates and pre-term infants and the infants from one month to 11 months of age for follow-up for at least 12 months, and so we're asking the committee: is the duration of

proposed follow-up at six and 12 months after enrollment for developmental growth and safety assessments -- whether or not that's adequate, and if not, what duration of follow-up safety assessment is recommended?

For Item No. 4, we're talking about infants one month to 11 months of age.

Four (a), and these are basically repeats of the previous question: are the efficacy endpoints chosen for this study acceptable? If not, please suggest alternative or addition clinically meaningful endpoints?

Four (b), are the specified trial design, including criteria, monitoring and assessments adequate? And if not, please suggest alternative or additional criteria, monitoring and/or assessments.

Four (c), are the safety endpoints chosen for Studies 3 and 4 acceptable? And if not, please suggest additional safety endpoints.

And 4(d), is the duration of proposed follow-up at six and 12 months after enrollment for developmental growth and safety assessment adequate?

And if not, what duration of follow-up safety assessment is recommended?

And finally, Question No. 5 asks about the pharmacokinetics and pharmacodynamic designs in studies that we've requested, specifically asking: are the study designs for the single and repeat dose pharmacokinetic and pharmacodynamic/pharmacokinetic studies acceptable? And are there additional and/or alternative assessments recommended for study of proton pump inhibitors in pediatric patients?

And I thank you, and we look forward to a good discussion.

CHAIRPERSON CHESNEY: Thank you, Dr. Raczkowski.

And for those of you who may not have heard, Dr. Murphy has given us permission to go until ten o'clock tonight if that's what it takes --

(Laughter.)

CHAIRPERSON CHESNEY: -- to answer all of these questions, but we can have our time moved to one o'clock, and we'll postpone this afternoon's meeting by an hour.

So let's start with the first question. Can the efficacy of a proton pump inhibitor for the treatment of pediatric patients less than one year of age be extrapolated from adults? Why or why not?

Dr. Nelson.

DR. NELSON: Intensivists are always willing to jump in. A question. I was impressed in reading through the materials about the differences in presentation, symptomatology, and the like within this population, particularly which I guess they're going by the term supraesophageal or respiratory.

My question then is -- to some extent follows from Dr. Hassall's, I believe, presentation that the hard endpoints that you suggested are efficacy endpoints that could perhaps be extrapolated, such as esophagitis.

So if you presume that the change in gastric pH has any impact on esophagitis, to the extent that you're advocating a hard endpoint, I would raise the question as to whether efficacy could be inferred once you've done the appropriate pharmacokinetic and pharmacodynamic studies.

If, however, you're looking at the supraesophageal and respiratory endpoints, it looks to me like you could not infer that since, in fact, that's not an adult presentation. So that would be at least my sort of working interpretation and question that would then come out of that.

CHAIRPERSON CHESNEY: Dr. Ward.

DR. WARD: In the background information, I thought there was some nice description of physiologic changes that matured around six months of age, and it's unclear to me that the one-year cutoff is appropriate, that maybe a six-month cutoff might be more appropriate to define a different population.

CHAIRPERSON CHESNEY: Dr. Kauffman.

DR. KAUFFMAN: I was impressed with that, too, and it reminded me we never do literature searches back beyond five years, rarely, and beyond ten years, never. But many, many years ago, when I was in Michigan, we did a study metoclopramide when it was a new drug in infants in the first year of life from one month -- two to four weeks was the youngest ones -- up to a year of life, who presented with GER

with complications, not just spitting up.

And this was a randomized, double blind, placebo with a weak run-in on nothing, and then they were randomized to two arms. They either got metocloparmide or not.

And simultaneous esophageal gastric pH was our outcome measure at that time, and then we did secondarily parent recording at home.

But the thing that struck me about this study was that in infants up to about four to five months of age, we could not distinguish between placebo and active drug.

In infants older than four to five months, then we had a statistically significant difference using this prophenetic (phonetic) agent in terms of pH outcomes, and we speculated at that time that this was due to the fact that physiologic reflux and with frequent feedings in the younger infants was obscuring, washing out any difference in the pathologic reflux, and by the time we got to around six months, the babies we were seeing were true pathologic refluxers, and the drug was having a

pharmacologic effect.

And it fits some of the other information that was described this morning. This maturation takes place around that time. So one of the risks of lumping one month to 12 months in one group is we're going to wash out, if there really is a change at around five to six months. We run the risk of washing out any efficacy that we might -- that might exist in that six to 12 month age group and not seeing it.

CHAIRPERSON CHESNEY: Thank you.

Yes, Dr. Blackmon.

DR. BLACKMON: I think one additional reason one should use some caution in this is the fact that there are so many different reasons for complicated reflux that occur in infants that do not occur in adults, and the reasons, particularly the neurologically impaired or those with anatomic disorders, would confound the efficacy issue substantially because it's not just acid reflux. It's the issue there.

CHAIRPERSON CHESNEY: Dr. Blackmon, would you support the six month cutoff that Dr. Kauffman and

Dr. Ward were talking about for efficacy studies?

DR. BLACKMON: I would have no problem supporting six months for term infant. Quite honestly, I'm not sure where the breakpoint is for the extremely pre-term infant.

We have a whole population of infants now that we still don't know what their maturational course is, and that's by and large the infants of less than 26 weeks' gestation, and they are a substantial part of our morbidity in the NICU.

I would say if one could ascertain a reasonable break point for that group, yes, but for a term infant, I would have no problem with the six month.

CHAIRPERSON CHESNEY: Dr. Ward.

DR. WARD: One of the important points that Dr. Blackmon made was these two categories, the child with esophtrialtresia (phonetic) and the neurologically impaired children that are frequently candidates for fundiplications and surgical intervention, and those children, I think, are almost universally recognized as difficult to treat.

Reflux is a significant morbidity for them, and I think we should actually think of those as a population that may warrant specific criteria for enrollment in trials.

CHAIRPERSON CHESNEY: So there might be two subsets of patients, the normal term infant maybe up to six months, and then the pre-term infant, and particularly those who have significant underlying disease.

Dr. Hassall.

DR. HASSALL: If I could just speak to a couple of the issues that were raised. I think that under the age of a year, as far as I can I determine, the only real hard endpoints are esophagitis and, slightly less hard perhaps, failure to thrive.

I see it being very difficult to have a good endpoint in the patient under one year of age, assuming that we are enrolling only patients with GERD, in other words, with GER disease, in other words, a complication.

So my response to Question 1 is I believe one can follow esophagitis or failure to thrive, but

they are relatively uncommon. I mean, we do see esophagitis in the six, maybe four month old to 12 month old child, but they have to have pretty severe reflux disease.

So, again, we're talking about what's reality in terms of being able to recruit patients to these studies, and do we have enough? And certainly I would doubt that we have enough to break it into a number of subgroups.

The other issue that I'd like to address is the issue of the zero to 12 months. I'm not sure that that is important if we are only enrolling patients with GERD. We're not trying to enroll patients who are thriving, who are just vomiting, you know, upwards of 95 percent of whom will get better spontaneously. We specifically don't want to enroll those patients.

So we really only want to enroll patients with a complication, and once they've got a complication, then you can assess efficacy.

CHAIRPERSON CHESNEY: Yes, Dr. Gold.

DR. GOLD: Actually I think Dr. Fink and

then I'll go after him.

CHAIRPERSON CHESNEY: Oh, Dr. Fink.

DR. FINK: My comment, I guess the concern I have as a pulmonologist and seeing the failure of NISN (phonetic) to correct problems is I really don't think we're dealing with GERD in the under six month old. I think we're dealing with feeding dysfunction, and it's a much more global issue. It includes maturation of upper airway reflexes, ability to swallow without aspiration, maintenance of the airway during sleep, and GE reflux often being one component of all of those elements of maturational and neurologic deficits.

But to cal lit GERD in the sense of gerd in older children I think is a misnomer. So I really think part of the problem is definitional, and Under six months really are talking about a feeding disorder or a feeding problem that may have GE reflux as part of its symptomatology.

And so I think the six-month cutoff does make some sense, and those are beginning to start out at that age, and the neurologically impaired child is

probably a poor one to study even above six months of age because if you look at supraglottic manifestations, you're going to have to put in some very strict criteria to rule out aspiration from above because it's sure seen in a number of failures of NISN to completely dissolve symptomatology.

CHAIRPERSON CHESNEY: Dr. Gold.

DR. GOLD: Okay. Two points. I think, first, it's easy to make the clear distinction -- I think this point was well heard -- that the patients with GI anatomic abnormalities really belong in their own special category. Those with neurologic injury belong in their own category, and then your, quote, unquote, normal.

But I'd like to sort of offer some provocative thoughts with respect to the issue of defining an age, and to use my esteemed colleague Greg Kerns' coin of words, I'd like three words: responsible, feasible, and applicable.

One of the things that I'd also like, and I said this to Victor in the break, is that this not stop here, that this be a continuing and ongoing

dialogue.

What this wonderful set of references, I think, highlights is a different set of perspectives from different disciplines, that of ENT neonatology, pulmonology, gastroenterology, and pediatricians about an entity that really is still lacking clear case definitions, is lacking good epidemiology, is lacking good issues with studies with respect to its natural history.

We can't really come to a specific definition of the right age to do the cutoff when we haven't really defined the case definitions and then have followed that over time so that we understand what we're looking at at the six month, one year, two year, and ten year old.

And I think we need to think about it with respect to responsible, feasible and applicable. We need to think about it because in the end what we need to do are studies that we can go back to our clinicians, and those of us who are clinicians who are going to be using these drugs anyway, we're going to offer the information that's going to allow them to

make appropriate and safe choices for drugs to use.

Secondly, for the parents of these children who -- my daughter had fairly significant reflux, both the destroying of the ties, but also the screaming at night -- and those that we're going to be asking to participate when we're giving them the informed consent form in these studies.

So I think that we need to think carefully about our cases, whether we're coming up with definable clinical correlates and objective, validated endpoints that then can be used in efficacy studies in these particular age groups.

And I think because of the advancement of technology and the fact that we are, you know, resuscitating premoids at 450-500 grams, we're dealing with a whole different set of populations that have a whole lot of co-morbidities that either need to be controlled for in a proper design or thought of in terms of contributing to the overall process of reflux.

CHAIRPERSON CHESNEY: Dr. Winter.

DR. WINTER: Well, I would like to really

commend and thank Hugo and Victor and their colleagues for focusing this agenda on a very important issue for our patients, and it's not because I have to leave early to go to my daughter's senior prom that I'm going to come to be somewhat definitive about my comments.

But I would propose to the voting members of the committee that efficacy studies in premature infants not be part of a PPI template, and I base that on the comments that Dr. Gold made, and I agree with what he said.

But apnea associated with GERD is controversial. As an outcome measure, it's affected by multiple factors, including CNS development, LES maturation, GI motility, feeding issues, cardiopulmonary disease, and the role of acid suppression in treating apnea is of questionable value.

And so I think that doing efficacy studies in this population is not feasible, and I don't think will give us the answers to those questions.

I think our responsibility to our patients

and to their families is to understand the pathophysiology of the disease and to encourage the NIH and the Children's Digestive Health and Nutrition Foundation to support RFAs to answer these kinds of questions.

And probably more importantly, I think our role is to educate practitioners about evidence based medicine and to have educational campaigns to do that because I have a sense what's driving the questions that we're being asked is use and not benefit.

And so I think that we need to separate the question about industry sponsored template for PPI from the pathophysiology and the educational needs that our patients need to have.

So I would urge the committee not to consider efficacy in the premature infants as part of the PPI template, but rather to encourage other means of addressing these questions.

CHAIRPERSON CHESNEY: Dr. Winter, I'm not sure when you have to leave, but may I ask you a question? If we don't consider the use of PPIs in premature infants, what population or is there any

population that you think we should look at efficacy studies?

DR. WINTER: Yes. I think that we should look at efficacy studies over a year of age. I think that children over one year of age -- reflux, I think, is a disease that begins some time in child -- adult disease begins sometime in childhood for many patients, and it's a disease that waxes and wanes, and the cycle of injury and repair over many, many decades results in complications of GERD in both adolescents and in adults.

So I think of the disease over a year of age in children may be the harbinger of sequelae of disease in older children. So those are the patients that I would consider efficacized to be critical in.

And, for example, in children over a year of age who have irritability, who are in pain, PPI therapy may be effective in those patients, and that's a population in which PPIs are being used, and it is possible to design studies using irritability or the evaluation of irritability as an outcome to assess efficacy of those medications, not in hospitalized

patients, but in patients who we see in our office and in whom we use PPIs on a regular basis as gastroenterologists.

You have to exclude conditions such as allergy and food intolerance, which you can do by pH monitoring, because children who have reflux presumably will have some abnormality in pH probe studies, and that will also give you some degree of PK and PD assessment.

So I think that's a population in whom efficacy studies are valuable, but I'm not convinced that efficacy studies have a role at this point in time in children under a year of age.

CHAIRPERSON CHESNEY: May I just take the speaker's prerogative and ask you one more question?

DR. WINTER: Yes.

CHAIRPERSON CHESNEY: You made the mistake of saying you were leaving.

DR. WINTER: No, I have until about 11:30.

CHAIRPERSON CHESNEY: I do a month of general pediatric attending every year, and this is the population that I understand the least about and

the ones that get us into the most trouble, and I'm particularly intrigued by Dr. -- not the most trouble, but where we're just, you know, pulling things out of the air -- and I'm intrigued by Dr. Hassall's comment that they reduced their anti-reflux surgery from 50 to five patients in one year. That's phenomenal to me.

But I'm also struck by how well the anti-reflux surgery works. I mean, something is being repaired in these infants.

And I feel like if we don't address this issue now, it's going to be several years down the road where we still don't have anything for these infants, and that's maybe a somewhat emotional response, but you know, of everything that I see on the general pediatric service now, it's these infants that we seem to understand the least about.

And I wondered if that would factor at all in your decision just to look at efficacy over a year of age.

DR. WINTER: Well, I agree with you. I think that this is a question that certainly needs to be studied. I'm not sure that this is a question that

needs to be studied by industry sponsored investigation.

I mean, I think that this is a very important question. It's a question that the NIH and foundations, such as CDH&F, which sponsor RFAs to answer these kinds of questions, should be sponsoring and should be asking these questions, and there should be well defined studies to look at the physiology and efficacy of these trials.

But I'm just concerned that the size of the studies are not going to answer the questions. The purpose of these studies is different, and I think that I'm just concerned that we're not going to get the information that we want to have by requiring this as part of a PPI template.

That's my motivation in saying the statement.

CHAIRPERSON CHESNEY: I understand. Thank you.

Dr. James.

DR. JAMES: I just wanted to follow up on Dr. Winter's comments, and I agree with him in that

the efficacy studies are very difficult to do in the children less than one year of age.

But I do not think that relieves us of our responsibility to continue doing the pharmacokinetic and pharmacodynamic evaluations because we know that we can do those types of studies. We have done those studies in HT receptor antagonists. We can use the same type of templates to study the PPIs in the children less than one years of age.

So that at least at the end of the day we have the dosing information, and we have the developmental maturation information to be able to provide to physicians and to families.

CHAIRPERSON CHESNEY: Thank you.

I have Dr. Hudak, Raczkowski, and Gold, in that order. Dr. Hudak.

DR. HUDAK: I guess I'd like to take a slightly different tact to that. I think that the studies in the premature babies for efficacy do need to be done. Whether they're done as a part of a written request here, whether they're funded by an HMO or NIH or whatever, I think they desperately need to

be done because there's no question in my mind that this class of drugs will be used with great frequency in neonates.

And to do that without any information on efficacy or safety, I think, is a mistake. We've gone down that path many time.

So as an advocate for our patients, I think that that information is critical. As difficult as it might be, you know, to design the studies, I do think that with relatively few number of patients you can have information as to whether or not the therapy is effective.

There is reason to suspend some disbelief here. I think that there's reason to think that it might be affected. As you point out, we don't understand very much about the association of reflux with apnea in a lot of these children.

I think there is some evidence that there is an association, although we can't get at it with the methods we've used thus far, but I think if you were able to demonstrate a decrease in those supraesophageal symptoms with the PPI class

medications, you know, that would go a long way towards stimulating a lot of the investigations in terms of pathophysiology and whatnot that you allude to.

But I think practically speaking, looking at our patients, without studies this class of drugs will be used and will be used relatively indiscriminately.

CHAIRPERSON CHESNEY: Dr. Raczkowski.

DR. RACZKOWSKI: I actually have a question, I think, for Dr. Winter, but before I ask the question, I just wanted to rephrase Question No. 1 in a way that may facilitate some of the discussion.

What the proton pump inhibitor template asks for in children greater than a year of age is not formal efficacy studies. It asked for PK and PD studies, and the assumption is there that if you know enough about acid suppression from blood levels and from pharmacodynamic studies, that the disease of gastroesophageal reflux disease is sufficiently similar between kids more than a year and above to allow us not to have to redo formal efficacy studies

in those kids that are greater than a year of age.

On the other hand, in kids less than a year of age, we've taken the approach that PK/PD is not enough; that if all you knew was about acid suppression of these agents in that age group of less than a year of age, that would not allow you to draw any conclusions about whether the drugs really work because the manifestations are very different in that age group.

And so I guess the question I have for Dr. Winter is: do you believe that there are specific differences between GERD in kids more than a year of age or so that would require us to do efficacy studies or if we know enough about acid suppression in terms of the PK and PD, is that enough?

Once we get the right dose, that gives us a certain amount of acid suppression. Would that be enough for that age group of more than a year of age?

DR. WINTER: Well, first, I agree with Dr. James about the benefit of PK and PD studies in all of the age groups. I think that that's very clear.

The question about efficacy over a year of

age, I think the pathophysiology is similar. The clinical presentation is somewhat different in that children over a year of age may have different clinical symptoms that need to be assessed, such as growth issues that may be important.

And children between zero and one year of age, the outcome of irritability is a major factor that's different than adults, but I think that the pathophysiology is similar.

So that efficacy studies over a year of age, I think, adult data is extrapable. Between zero and one, I think that there are differences in terms of the clinical manifestations that we should be studying in terms of efficacy, and in premature infants we already discussed that issue.

CHAIRPERSON CHESNEY: Dr. Gold, you were next.

DR. GOLD: I actually am not sure that I necessarily completely agree. I think that we still don't know enough about manifestations in that over one to 11 year group to completely say that we can extrapolate all that is learned in adults to that.

I agree and would like to echo Dr. James' comments that I think there is the importance of doing the PK/PD in the less than one because at least with that we can say -- and safety -- we can say we can offer a safe dose. Whether or not it's effective is not clear.

And I think, you know, your comment about the fact that the fundo.'s (phonetic) work is an interesting point. Fundiplication rates, when one looks at the pediatric hospital information system, which is probably 32 children's hospitals across the U.S., have risen dramatically from 1995 to the year 2000 and, in fact, have grown exponentially even though the rate of GERD admissions, which is four percent of all hospital admissions, as any diagnosis in the year 2000, it has gone and exceeded that of GERD, particularly with the fact that the lapnissen (phonetic) now, which the first report was in '95, is available.

And yet you look at the literature, and there's a complete paucity, I guess -- that's a sort of an oxymoron -- but there are no studies that look

at outcome or long-term natural history of the fundiplication and what you're doing long term with these children.

So I think that the surgeons are going to continue to do fundiplications, and those of us who would try to, you know, use appropriate, as Dr. Hassall pointed out, case selection in those patients that go to surgeons, we need to have good data that then we can use in terms of applying appropriate medical therapies and maybe non-medical therapies that will help our children both at the time and then long term.

CHAIRPERSON CHESNEY: Dr. Hassall and then Dr. Nelson.

DR. HASSALL: A couple of questions. Just to address the fundiplication issue first, there are very -- there are lots of data in the surgical literature about the success or otherwise of fundiplication in children, and while they may work acutely -- and I can give you these published data and summaries on them -- the longevity of fundiplication in all handicapped children, esophageal atresia

children, and children without any underlying disease is astonishingly short.

The surgical studies go no more out than about five years at the absolutely maximum, with no physiologic parameters to determine their success or otherwise, and the failure rates within a year to two years are staggeringly high, you know, 30, 40 percent easily, and in the high risk groups, higher than that.

So I think we are really looking -- not that I don't refer patients for fundiplication, but we select them in the particular way that I mentioned earlier.

So I think that really fundiplication has a role, but I think that the degree of consideration we're giving to PPIs actually in many ways speaks to the failure of fundiplications, and even when it works, these children have some problems.

I'd just like to get back to Dr. Raczkowski's questions, and that is I echo Dr. Winter's comments fully. In the under one year old child, once you enroll a patient with a complication, it doesn't matter if 90 percent, 95 percent of

children who are healthy get better by the age of a year or two years. We're only enrolling or thinking about children who need PPIs, hopefully, who have a complication.

And once they have a complication, and especially I think we'll find if we study those under one year olds, the great majority of kids with esophagitis and/or failure to thrive and/or chronic cough, et cetera, et cetera, are going to come from two groups: esophageal atresia and neurologic impairment.

And in our studies, upwards of 50 to 75 percent of all of the children, even in the older age groups, have come from those groups when we select out others.

So once we've got those children with esophageal atresia or neurologic impairment, I would extrapolate to the under one year of age from one to two years of age or three to four years of age or eight to ten years of age if they've got esophagitis and failure to thrive or chronic cough.

The kids under one year of age -- and I'm

specifically excluding pre-term infants; I'm talking about zero to one. I think pre-term infants is a different discussion.

I would feel that one can easily extrapolate the pathophysiology and the consequences of reflux in the zero to one year old from the two to three year old, from the older child. And we've shown that PPIs in several studies, lansoprazole, omeprazole, many, many studies, long term and short term, can treat these.

As long as it's an acid related disorder, we've shown that acid suppression in adequate dose can work. So I would definitely propose assuming efficacy under the age of one year from not even -- perhaps it's too scary to assume it from adults, but from five year olds, from ten year olds, from 15 year olds.

CHAIRPERSON CHESNEY: Thank you.

Dr. Nelson.

DR. NELSON: That actually leads in nicely to the comment I wanted to make. The scientific discussion we're having has an underpinning of an ethical principle, which is that children shouldn't be

exposed to unnecessary risk.

And if one could extrapolate efficacy, then you shouldn't have to do studies of efficacy that might involve such risk.

One concern I have is that there is, for example, five drugs on the list of PPIs that are used in this population, all of which are on the list of having received a written request. The question I want to put on the table is that, in fact, we should be willing to extrapolate efficacy from a study in pediatrics using the same disease and the same drug class to another study in pediatrics.

And it would concern me if we're, in fact, having the fifth or fourth or third company doing what one and two had to do. The first efficacy trial for the first drug should be applied to a modification of the written request for Drug 2, Drug 3, Drug 4, Drug 5.

That's how IRBs are going to review this. We're going to see what's labeled, what's available, what's being used, and just ask the question: do we really need to do this in kids for another one?

So I think that's something I'd like to put on the table that needs to be part of the discussion.

CHAIRPERSON CHESNEY: Yes. Dr. Ferry.

DR. FERRY: I think that my clinical experience is a little bit different from what Dr. Hassall mentioned. We certainly see a lot of children in the first year of life with neurological impairments, esophageal atresia and problems that lead to really severe reflux disease.

But we also see in our practice a lot of children who are not thriving, who are drying, are really poor feeders, irritable, all of the same spectrum that older children will complain of heartburn, and you know, to me it's the same disease.

So I don't think it's just these other complicating diseases that are the most common presentation in our own practice.

I think his point that we might well be able to extrapolate from older children to the one year of age I think is a really good point. I really think these children in every clinical sense seem to

respond the same way a two year old, a three year old, a five year old does.

And we can document the fact that they actually have esophagitis. It may not be erosive. We can document pH changes.

I think the question to me really comes back do we actually need the efficacy studies in that group of patients.

CHAIRPERSON CHESNEY: Dr. Ferry, do you think we need any efficacy studies in children?

DR. FERRY: Well, I think certainly when you get down into pre-term infants, there I think that's a different group of patients totally, but I think, you know, if we knew the dosing -- I mean, my clinical judgment tells me these drugs have made a huge difference already, and there's a good bit of data out there.

I mean, do we need efficacy? I almost hate to say no to that. That seems like it's probably the wrong approach, but in fact, clinically these children respond the same way older children do. Even at three and four months of age, we have patients

referred all the time that have failed all the standard positioning, taking feedings. I mean, you can take all 13 people in our group, and they are absolutely convinced that these drugs work.

And we have the endpoints, you know, to measure that already. We see esophagitis. We do end up scoping, you know, a number of these children.

I think dosing, you know, is important. I think to my mind efficacy, there's a lot of data out there that says these drugs work in this first year of age.

CHAIRPERSON CHESNEY: Dr. Ferry and Dr. Hassall, it sounds like you already have a wealth of experience with these drugs, and from your vantage point, the thing that you need is PK and PD information. Is that a fair statement?

DR. FERRY: One of the first studies I ever did was on tube feeding in children with failure to thrive in reflux because we didn't have any -- I'm older than most people here. So it goes back a long ways -- and we don't do that anymore at our institution.

This used to be standard treatment. Failure to thrive from reflux, you put them on tube feeding, small volumes. They gain weight. Their reflux gets better.

We don't have to do that at all anymore because of PPIs. I mean we just don't do it.

CHAIRPERSON CHESNEY: Can I just write down the dose you're using?

(Laughter.)

CHAIRPERSON CHESNEY: Dr. Hassall.

DR. HASSALL: Yeah, I think the studies have been done. I think we already know not just from personal experience, but from published studies that these drugs work in older children from one year up.

And so I don't think we need to reinvent, to rediscover the efficacy, that these drugs are efficacious.

I fully support Dr. Winter and Dr. James and everybody else who said that we do need PK studies because I see these as dosing and safety issues.

I don't see efficacy issues on the table for children who are in the age group we're talking

about right now.

CHAIRPERSON CHESNEY: Dr. Ward.

DR. WARD: It sounds like among the pediatric gastroenterologists there's relatively good agreement that the signs and symptoms of erosive esophagitis disease is similar in the young infant as it is in the older child. Would that be the group that there would be agreement that the efficacy is not needed in that group, excluding, again, the pre-terms?

DR. HASSALL: I'm sorry. Is the question that just --

CHAIRPERSON CHESNEY: I think the question was: would you both agree that efficacy studies are not needed in any age group which has -- and please correct me -- classic adult GER disease manifested as irritability instead of pain and some degree of esophagitis; that we don't need efficacy studies in children?

I didn't phrase that as well as Dr. Ward.

DR. FERRY: Well, no, if I understood the question, it was talking about erosive disease, and that's not the predominant disease in children. You

can demonstrate esophagitis by biopsies. You can demonstrate acid reflux. I think erosive disease is actually not the most common form.

DR. WARD: Yes, that was probably a neonatologist misspeak.

(Laughter.)

DR. WARD: So I guess I would say esophagitis disease: irritability, pain, sometimes refusing feeds.

DR. FERRY: Yes.

DR. HASSALL: Yeah, plain and simple esophagitis, histologic and/or gross, yes. But I would extrapolate and say that if a disease is acid related, then these drugs are going to work, and we already have efficacy and safety data with hard endpoints.

So, you know, we might debate whether or not respiratory disease is or is not due to acid at all or whether it's due to volume reflux. But if it's an acid related disease, we already know that these drugs work in acid related disorders, and we have pH studies to prove that, as well as other endpoints.

CHAIRPERSON CHESNEY: Dr. Wilfond, and then I have Dr. James.

DR. WILFOND: You know, looking at it from a point or perspective, I want to echo what Bob Fink had said before because I understood his comment to be in the opposite vein, that the issue for those children with complex problems, and that includes some pulmonary manifestations, perhaps some subtle neurological impairments, are sufficiently complex that it may be even harder to tell efficacy when it exists.

That's what I thought I heard you say, and I think you were trying to make a claim that even an attempt at doing efficacy studies may be challenging, but at the very least, I think that I would want to say that for that population, I think efficacy studies are necessary to sort out to what extent these types of drugs are helpful in that population.

CHAIRPERSON CHESNEY: I had Dr. James down. Do you?

Dr. Winter.

DR. WINTER: I think that what Dr. Hassall

said is precisely the point from a GI standpoint, that if the disease is acid related and we know the right dose to suppress acid, which is a critical component, then we believe that the medications that we have are effective.

The question about asthma and, you know, other pulmonary disease is much more complicated because of the multi-factorial nature of the diseases. And you know, I think the question is not so much about PPI efficacy. The question is: are these diseases acid related?

And the question is whether or not that's an appropriate thing to include in a PPI template, and that, I think, is the essence of the question.

CHAIRPERSON CHESNEY: Thank you.

Dr. Spielberg.

DR. SPIELBERG: Yeah, I think it sort of gets to the heart of the whole thing. When we think about extrapolation of efficacy, we have to have an understanding of mechanism in order to be able to extrapolate efficacy. So clearly for the acid related issues that are clearly acid related, the issues of

PK, adequate acid suppression, and safety and formulation so that you can accurately and appropriately give a dose are really the heart of the matter.

What I'm hearing from the discussion because I think all of us are worried about youth in other situations, and that includes both patient populations, such as the neonate, and other indications. I'm hearing a fair amount though that in terms of valid endpoints to design some of these studies, that we really don't have them, and that brings up several issues, not only a failed study potentially where there may be efficacy and we're just measuring the wrong thing because we don't have the science, but it also brings up ethical issues because if we're going to design studies with endpoints that we really don't believe in to enroll children in such a study when we really don't have confidence that that study is going to give us an interpretable outcome raises some real issues for me.

I agree with Harland that we need those data. We have an obligation to all of our patients in

whom a drug like this is currently being used.

And I agree, too, that we have a long way to go to develop some of the endpoints from an NIH perspective or from a pediatric GI community perspective, to give us endpoints we can use, which may say -- and not to confound age populations and cornicity -- it may be premature to ask for certain types of studies until, indeed, we have enough understanding.

Are these acid related? If they are acid related, then we'll be able to extrapolate. If the data show that they are not acid related and they're still being used, then one has to question why the drugs are being used in the first place.

So there are two levels here. One is the desperate need to get the data, and there are a number of mechanisms which have been suggested today, and then the second is the issue and the confounder here of the incentives.

And just to make some comment about use of the Best Pharmaceuticals for Children Act and such, I think all of us agree that because, indeed, the

incentives cover the moiety as a whole, this is a good opportunity to study conditions outside the adult situation where efficacy studies would be needed in unique pediatric diseases.

And I think this is one of the things that was in the back of everybody's mind, including Congress, to give a mechanism to insure the diseases outside adult diseases can be studied.

The flip side though is if we don't yet have tools to adequately do those studies or if they are questions about those tools, I think we then have to seriously consider whether that should be part of the template or go into something like an NIH mechanism which will provide those data in the long run.

CHAIRPERSON CHESNEY: Thank you.

Dr. Gorman, you had your hand up.

DR. GORMAN: I always dread speaking after Dr. Spielberg.

CHAIRPERSON CHESNEY: Sorry. Next time I'll ask you first.

(Laughter.)

DR. GORMAN: Thank you so much.

I always enjoy listening to my colleagues who look at the other end of the telescope. They get the people who have been screened by the parents and then the pediatricians and perhaps another specialist before the eventually end up in your special areas of expertise.

These drugs will be used for every spitter that comes down the line, every fat, happy spitter. I would be delighted to see an efficacy study with a high rate of failure so that the pediatricians in private practice will learn which groups not to use these drugs on because I agree that the dissemination of information for both successes and failure, if it is so targeted to only be the acid disease which makes up some fraction of reflux disease, then it will be meaningless because it will get generalized as it gets detailed out to the community as being a treatment for reflux.

And reflux is like pornography. No one can define, but we all know it when we see it. And I'm listening around this table, listening for hard

output, hard endpoints, and I hear a few that I think we all agree on, and then there's a lot of very fuzzy ones that we don't agree on.

I think efficacy studies are necessary because it will show us our ability to define the conditions on the way in, as well as define our endpoints on the way out.

Thank you.

CHAIRPERSON CHESNEY: Dr. Nelson and then Dr. O'Fallon.

DR. NELSON: I guess my question would be: what is the mechanism currently for the dissemination of the negative results of such a study? If the clinical indications have defined our cases, presumably if it's not pH related, we would end up with a negative study. If it's negative, I mean, there are existing requests out there.

I didn't check to see if anybody has -- well, I think one has gotten exclusivity. So the question would be: was that study negative? Did it use a clinical case definition? And if it was negative, do pediatricians know it?

I'll confess I didn't check the labeling to see if that has been disseminated in that way, but has that bene published as a negative study?

Because this all assumes the negative study would get out into the general pediatric educational materials. So I guess that's a question of adequate dissemination.

Often negative studies just disappear and don't get published and don't result in labeling.

CHAIRPERSON CHESNEY: Dr. O'Fallon.

DR. O'FALLON: When I came into this, I was very concerned about the endpoint issue just on the basis of all the stuff that we got from the FDA, and today it made it even worse for me listening to the facts presented.

So I do think if you don't have good endpoints, there's no way to get a good study. So I think that is the major issue here.

But if you can agree that there are some useful, maybe not optimal, but useful endpoints, especially for the acid associated reflux, then I think that the suggestion of having the randomized

withdrawal study is very good.

I think that probably comes close to being an optimal design because what's going to happen is you're going to be able to get at some estimate of what percentage of the population do not respond at all. They will never be randomized because the drug right up front doesn't do any good for them.

And the ones that do respond, then you can withdraw, and I am assuming you would switch to a placebo and do a double blind. I'm assuming that it would be that sort of thing.

But if you switched half of them to a placebo and continued the study, you'd get an idea whether it was the drug that was doing it or whether it was some other underlying thing, such as maturation that's going on.

So I think a randomized withdrawal study with a double blinded placebo deal would really help to provide a lot of useful information about what's going on.

CHAIRPERSON CHESNEY: And that moves us to the second issue, and I wanted to ask Dr. Raczkowski

if he wanted more input on the first question.

Dr. Fink, did you have something addressing the first one?

DR. FINK: Well, Dr. O'Fallon, I guess, just raised a red flag in my eyes in terms of study design, which is it's well known with esophagitis that if you used a withdrawal of placebo withdrawal design, if you take children who are symptomatic at enrollment and you put them all on an effective acid blocking agent for eight weeks, you're going to heal the esophagitis in many of those children, and you will then get a false negative result because you'll withdraw them onto placebo.

And depending on the length of time they're on placebo, they may be asymptomatic even though the drug was highly helpful to them during the non-randomized run-in period because your eight weeks may heal their esophagitis.

CHAIRPERSON CHESNEY: Excellent point.

Dr. Raczkowski, we haven't given you a definitive -- I mean, many, many concerns were raised, and I think we all share those. Do you want us to go

on to number two and assume that there's some population or --

DR. RACZKOWSKI: Well, let me just make a quick comment. I think that the agency by and large agrees that for acid related conditions, that these are effective drugs and that, therefore, if you could find the right dose by doing PK and PD, that that would probably be sufficient.

I think that the concern is that they are oftentimes being used and for what may or may not be acid related diseases, and that was the intent for the request of the efficacy in those populations.

But I think the discussion has been very, very helpful.

CHAIRPERSON CHESNEY: Dr. Murphy.

DR. MURPHY: Would it be fair to say at this point that the discussion has indicated, as Victor just said, that for acid related diseases we don't need efficacy trials for any age group? Is that -- I'm trying to summarize what I think I've heard here.

And then when we get into the cutoff of

under a year, what I thought I heard was that we really don't think that's a good cutoff. We felt that basically the diseases that we were discussing that we were concerned about really were the respiratory related, pulmonary related, other diseases that occur in the younger age group, and the issue is: what are those diseases? What are those endpoints that we're going to be looking at? And is the age cutoff six months or lower?

So that's what I've sort of heard thus far.

CHAIRPERSON CHESNEY: Dr. Hudak, maybe you could help us with this. Do you feel like there are situations in the premature age group in which we do need efficacy studies for these agents?

DR. HUDAK: I think the answer in my mind to that is yes. I think, you know, we all struggle with endpoints, but you come back to the situation of why is the clinician starting a premature baby on his medication. Okay?

The answer is not we've got a pH probe that shows the pH is acidic. It is not we've got

impedance technology that shows the baby is refluxing. It is not that the baby is regurgitates formula on, you know, the bed.

The reason a clinician starts the baby on these medications is because the baby has frequent, serious, significant apneas, bradycardias, and desaturations. That is -- Bob, would you agree? -- I mean, that is the answer.

DR. WARD: That's what our survey showed. It was pretty staggering.

DR. HUDAK: Right. And they don't study to define whether it's reflux, whether reflux is present or not. So what I think would be good, and I think those are pretty hard endpoints that we deal with clinically, and if you were to demonstrate that this therapy reduced those episodes from six a day to one a day, that is a significant improvement.

I think while they're doing the study there are other things that need to be looked at in terms of mechanism to make it efficient and to make it the best study possible for our patients so that we have some idea of what we're doing, but I think, yes,

efficacy studies are needed, and, yes, the endpoints are fairly clear, fairly reproducible, easy to assess and interpret.

CHAIRPERSON CHESNEY: Dr. Ward?

DR. WARD: The problem I see with that is the complex causes of apnea and the multiple ways that may lead to apnea as an endpoint and the multiple diseases that may lead to apnea as an endpoint.

When I had read through everything, I thought that the withdrawal trial, the withdrawal design was not a good one, but if, on the other hand, you use apnea as the endpoint and you only continue to study those children who have shown a positive response, it provides enrichment of the sample population, and I think it can get to the answer then about safety and efficacy more effectively.

This is how the drugs are being used, but I think there will be almost a ten to one treated versus responder ratio. That is, I think there will be a lot of kids with apnea that will not respond, but we don't recognize that clinically.

CHAIRPERSON CHESNEY: Dr. Winter and then

Dr. Hassall.

DR. WINTER: In terms of the children between zero and one and over a year of age, I think just to clarify what Dr. Murphy said, and I agree with her, that if we know that a disease is acid related or if a child has acid related disease, we can assume that the therapy will be effective, that there was adequate efficacy.

The challenge is identifying those patients in whom there's acid related disease and, for example, children who are irritable. Some of those children are going to have food allergies and they're respond to being put on an amino acid based formula, and their irritability will get better.

Some of those children -- but if you exclude those children and you identify children who have delayed acid clearance or who have esophagitis, then PPIs should be effective therapy.

The problem I have is the statements by the neonatologists about the use of PPIs in children who have apnea and bradycardia in the pre-term infants. Because what I hear you saying is you don't

have any effective therapy, and so because you don't have an effective therapy and you don't have any idea of what efficacy outcomes you need to measure, that you use whatever comes to mind or whatever is available, and you're not practicing evidence based medicine.

And that may be the reality of what happens in the NICU. I understand that. There's a certain practical aspect of what you do, and sometimes I put patients on probiotics because I think its going to help their diarrhea, and it may or may not be effective, but I would like to hear you define, you know, how you would do a study that's going to answer that question because I don't think it's necessarily in our patients' best interest or the family's best interest to enroll patients in clinical trials of efficacy in pre-term infants for which there is no adequate outcome and for whom we're not going to get the data by doing those studies because of all the confounding variables.

If you have a study design that will answer that question, then I think it's reasonable,

but so far I haven't heard that.

CHAIRPERSON CHESNEY: Dr. Gardener had a question for the group or comment.

Use the hot mic.

DR. PEREZ: Could you either come to the podium or use this other mic? Apparently the sound person walked out on us.

DR. GARDENER: Proton pump inhibitors have been available for approximately 20 years, and there's a great deal of intellectual fire power and expertise from the pediatric GI community on the panel today, and my question is: why haven't you answered these questions if the questions are so important?

(Laughter.)

DR. GARDENER: Now, one possibility is maybe suitable methods don't exist to address these very important issues and to the extent that's your answer, to what extent do you want to commit pharmaceutical and biotech companies to conducting studies for which suitable methods don't exist.

On the other hand, if your answer is you've got a lot of terrific ideas and you believe

they are good ways to address these issues, but you can't get funding, then to the extent you think that's the answer, then it might be appropriate to focus on given adequate funding, which is really what we're talking about here -- the funding won't be an issue -- how would you best want to design the study.

DR. WINTER: Well, I don't want to get going on why we don't allocate resources to children in this country because we'll be here until past ten o'clock tonight, but you know, I think that there's not been a lot of interest either from industry or from the government in terms of supporting clinical trials in children, and there are a lot of reasons for that.

It's changing now, and I think it needs to change quickly because we need to do these studies to get these data for these patients, and, you know, hopefully that's one of the outcomes from this type of a meeting.

CHAIRPERSON CHESNEY: Dr. Kerns.

DR. KERNS: I'd like to question Dr. Hudak, if I could, and please forgive me. I'll try to

phrase this without dealing with the sensitivities of neonatologists.

When you as a clinician make a decision to commit an infant with apnea and bradycardia to a medicine that modifies gastric acid, what is your goal?

Now, let me answer what I think your answer is. Because you believe it's less onerous for that baby to aspirate an acidic fluid into their lung than it is a nonacidic fluid.

These drugs do not have any impact that I know of on motility, and so the driver for the decision is always, in my mind, what it does to gastric acid.

Now, maybe Dr. Ward has some data on showing that changing gastric acid impacts the amount of time somebody refluxes. Am I missing the pharmacology link in terms of mechanism?

DR. HUDAK: Let me go back and clarify a couple of things. One is that, first of all, I'm not for Dr. Winter. We're speaking for the general neonatology community. I don't think that Dr.

Blackmon or Dr. Ward or I are necessarily representative in all aspects of that community, but we just deal with reality as we see it.

With respect to your particular question, you know, on these drugs, I think that the neonatologists around the table would not use these drugs in a baby who had apnea and bradycardia because we have no efficacy data, and we, the people around the table here, tend to be therapeutic nihilists and to practice evidence based medicine.

The reality is that I think a large number of our profession are perhaps more enamored by the potential promise of the drug, and they're also seduced by the possibility that they could do good for their patient maybe by using this drug. We tend to be more restrictive.

In terms of the study design, clearly it gets back to the patient selection issue that I mentioned to begin with. I think that the criteria for enrolling premature infants in an efficacy study will clearly be persistent apnea, bradycardia, desaturations that are unable to be managed by

standard therapy, together with some evidence, preferably, actually exclusively by pH probe that the baby is having acid reflux. Otherwise, it's really impossible to justify using a PPI agent with any rationale that that's going to have any efficacy.

So I think if those criteria could be met, I think an efficacy study could be done whether it's a traditional placebo controlled or whether it's a run-in, randomized withdrawal. I think both have their positive points, and I think that one could get some answer.

CHAIRPERSON CHESNEY: Dr. Ward.

DR. WARD: I would disagree with that. The other aspect is -- what we hear on rounds frequently is a child having severe apnea needing to be stimulated or bag mask resuscitated, and it follows an emesis, and that clinical scenario plays out a lot.

And I think to go back to Dr. Winter's comment, if you designed a trial in which there was a run-in period and you then withdrew only in those infants who had shown improvement in the symptomatology that you were associating with reflux

and esophagitis, then I think you could do an efficient trial.

I think there will be a large number during the run-in period that do not show a response.

CHAIRPERSON CHESNEY: Back to Dr. Murphy and Dr. Raczkowski.

What I think I'm hearing is that we don't need efficacy studies in children for a disease which is clearly acid related, but we're not exactly sure how to define always clearly "acid related."

But what I do hear is that there are two to three populations where we don't know whether preemies would be, with all of the manifestations that we hear about, would benefit by having an efficacy study with these drugs, and also the infants with esophageal atresion and neurologic disorders, that we might benefit by having efficacy studies there.

And I'm wondering if other people would comment on whether I've totally misheard this, and maybe then we can move on to potential study designs if these are populations in which efficacy studies might be done.

Dr. Hassall.

DR. HASSALL: Dr. Chesney, I was actually making the point with esophageal atresial and neurologic impairment that the studies have been done in the two to three year olds, eight to ten year olds, and so I'm proposing not redoing those efficacy studies.

But I wondered if I could just address a couple of the points that have been made by other speakers.

Just a general comment, first of all, that acid suppressing drugs work in two ways. They don't just work by treating purely acid related disease and changing the pH. They decrease your 24-hour intragastric volume.

So if a child secretes about one cc per kilo per hour and an adult about maybe two to two and a half liters a day of gastric secretions, if the pylorus, the anti-pyloral unit is then presented with a low gastric volume, intragastric volume, that will indirectly facilitate gastric emptying, and actually this has been shown in a study in adults in

Gastroenterology about two years ago.

However, I really wanted to focus on the issue of studying the pre-term or acutely sick children. I think we already have a safe drug for treating acid related disease, and that's IV renitidine, and if you can show that IV renitidine causes a change in intragastric pH and that is accompanied by a decrease in ABCs, in apneas and bradycardias, then I'm not sure that we need to trial in new drug because we know that renitidine is safe in that age group.

As Dr. Hudak pointed out earlier, he reduces when he's on service the drugs perhaps from 15 to ten drugs, but we're nevertheless dealing with an extraordinary number of variables, and I think to extract from that drug effect that we can attribute to PPI is going to be very difficult, not to mention the other conditions that affect pre-term infants.

So I'm not even sure we need a new drug for this, but even then, if we document apneas with pneumograms, it's extraordinarily difficult in my experience and from my reading of the literature to

even relate that to an antecedent reflux event.

So I think we're actually dealing with two common circumstances which overlap, and I would think it would be extraordinarily challenging to design a study in pre-term infants, all sick newborns, that would actually answer the questions at hand.

And so in these circumstances, I really don't find an answer for a useful endpoint. I think there are just too many confounding variables.

DR. WARD: Could I just respond to the issue about renitidine?

There are some neonates who have demonstrably or measurably low gastric pHs in whom very high doses of renitidine are ineffective at raising that pH, and in those infants, they do respond to PPIs.

So there is still a subset of neonates who will not fully respond to the H_2 blockers.

DR. HASSALL: So are those published data?

DR. WARD: Don't know. It's my personal experience. I don't know what Mark's is.

DR. HASSALL: No, no, no, just in terms of

saying that they didn't -- I mean, we know that tolerance does develop to IV renitidine, at least in extreme short bowel syndrome in published publications.

But if you're saying that sometimes renitidine doesn't work, but PPIs do in newborns, but this is not on the basis of publications, right?

DR. WARD: No, no. It's just some clinical experience.

CHAIRPERSON CHESNEY: Dr. Spielberg, and then I have Dr. Fink and, I think, Dr. Gold, you had a question a way back, and I didn't write it down. Dr. Spielberg.

DR. SPIELBERG: Following up on the issue of what we know and don't know in terms of designing a trial, Dr. Ward, you sort of indicated that if you just took all apnea kids, maybe ten to one, other etiologies or somewhere in that neighborhood, do we know enough about stratification, say, methylxanthine resistant, et cetera, et cetera, to make any kinds of reasonable judgments of what proportion of the patient population we would define after that would likely to

have an acid related mechanism because that has immediate implications for how you design the study, how you power it, how many patients you're going to need, et cetera, et cetera.

If it's still a very high, false rate of patients who are likely to respond even in an enrichment design some people would have responded to placebo anyway. So the numbers become extraordinary, and you really wonder of that population do we currently have the technology to define any better those kids who are really likely to respond to an acid expression mechanism.

It's a question to the neonatologists because, I mean, in terms of study design, we've got to have that if we're going to make any kind of rational approach designing a study.

CHAIRPERSON CHESNEY: Dr. Blackmon is going to respond for the neonatologists.

DR. BLACKMON: Well, a suggestion. One additional criteria for entry might be a history of recurrent infiltrates on X-ray not otherwise explainable.

We do have that phenomena in pre-term infants. I would say the sequence of changing the feeding, usually advancing the volume, increasing the handling, sudden emergence of these phenomena of infiltrates, and episodes of apnea and bradycardia that are very profound and frequently associated with emesis, but that is a small population of patients.

In my experience in a unit that admitted about the range of 100 to 120 infants a year in the less than 1,500 gram birth weight category, we might encounter that two or three times.

CHAIRPERSON CHESNEY: Dr. Fink, you had one?

DR. FINK: Well, I guess my comment -- it addresses a little bit Dr. Spielberg's concern. The other approach would be to be very empiric and do a randomized controlled trial in the use of PPIs in a selected group of premature infants to see if it decreases their time on oxygen, decreases time in the nursery, decreases the incidence of apnea. Because I don't think we can define the exact mechanisms easily by which all of these will occur. Yet they occur

commonly enough that the potential of looking at this as a therapeutic intervention might yield interpretable results, and you would at least have definable endpoints.

DR. SPIELBERG: The question I still have though if you took all comers and only two or four out of those ten had a mechanism that at all possibly related to this, you'd never see it, and you'd lose the opportunity to actually define those patients who would benefit just because of the numbers.

And I don't have a good enough feel in today's nursery situation what the expectation would be, whether it's going to be one out of ten kids that's going to really respond to this or two out of ten or maybe eight out of ten, and that's what I'm trying to get a gestalt for.

DR. FINK: I guess as a pulmonologist, things that have been demonstrated it is clear-cut that acid aspiration is far worse than nonacidic aspiration. So if you're looking at premature lung disease in a global sense, you could say suppression of acidity in premature infants maybe of some real

long-term benefit in terms of their overall pulmonary status, including apnea feeding and lung development, and it would be at least a tenable hypothesis with measurable outcomes.

CHAIRPERSON CHESNEY: And an infectious disease person would worry about intestinal --

DR. FINK: Sure.

CHAIRPERSON CHESNEY: -- and sepsis.

(Laughter.)

CHAIRPERSON CHESNEY: I have Dr. Gold and Dr. Luban next. Dr. Gold.

DR. GOLD: Lest we forget the advances that have been made in this, again, as an IRB member, Vice Chair, I think I should raise this from an ethical standpoint, too. Let we forget the advances that have been made by clinical efficacy studies in a lot of other disciplines.

We need to not completely dispel the fact that doing the right thing for our patients. We don't completely exclude efficacy studies. I actually really appreciated, Dr. Gorman, your comment as the clinician out there in the trenches in terms of what

data is going to be important. When we talk about what we're being responsible for, what are we going to give information that's going to go back out to the community physician who's got to deal with these parents so that they're giving safe and effective therapy to treat diseases.

The other thing that you have to realize is that although we've been speaking sort of from a narrow focus, at least as gastroenterologists, I mean, there are acid related disorders that result from acid refluxate into the lower esophagus that have manifestations outside.

Neonatologists are talking about apnea and bradycardia. I think, Dr. Fink, you've been alluding to other things, and that, again, thinking about careful case selection and appropriate efficacy studies where in those specific disorders where adequate acid suppression actually can be a very effective and safe mechanism for preventing those.

So I think we need to think about those as well in terms of how we're selecting out our populations by completely eliminating efficacy studies

or before we do that.

CHAIRPERSON CHESNEY: Dr. Luban.

DR. LUBAN: I was just wondering if the neonatologists could comment at all about the use of something like a SNAP-2 or a modified SNAP-2 to use as a clinical efficacy tool.

DR. WARD: You mean just using the acuity tool?

DR. LUBAN: Like a modified acuity tool later on.

DR. WARD: I think, again, it's too nonspecific, and I think, again, back to Dr. Spielberg's comment earlier, is that if you begin with a group of infants with apnea or apnea and suspected reflux and during the run-in period you only continue those infants in the trial who have a positive response to your intervention, that degree of enrichment makes the trial actually, I think, feasible, Steve, because those will be the only ones that continue on into the detailed monitoring during withdrawal or continuation.

CHAIRPERSON CHESNEY: Dr. Wilfond.

DR. WILFOND: I had three comments on three related issues. The first is this question of whether or not the efficacy studies are needed, and I think I've heard two very conflicting points of view. The first is that we don't need them because we already know that they're efficacious, and the other one is that we don't need them because we can never find out whether they are efficacious.

And those are two very, very different perspectives, and we need to -- so I guess what I want to do is focus on at least for those groups where we need to know about efficacy, but it's hard to do. AT the very least in addition to the premature hospitalized population, I would want to remind people about the category of those infants between one and 11 months of age, whether they're children with chronic lung disease or the child who comes into the general pediatric floor because of recurrent wheezing, and often it's blamed on reflux and they're put on anti-reflux meds.

I think that's a population where we are in need of guidance. We do things without knowing

what we're doing, what we think we do.

The challenge though, and this is my third point, is that it really is hard to measure this, and I completely agree with the people who are concerned and used the word "endpoints" euphemistically to mean we can't measure it because I think those -- and whatever the endpoints are, they are difficult to measure.

And the thing I want to get at is just if we're talking about things related to apnea, apnea is a very subjective measurement, whether it's an observation by a nurse or by a monitor, and I think the details we have to grapple with, but that's not a reason not to say that we shouldn't try to figure out who to do it.

CHAIRPERSON CHESNEY: Dr. O'Fallon.

DR. O'FALLON: For what it's worth, listening to this discussion, it sounds to me like the children less than a year do need to be studied, but it sounds like they need to be stratified as from one month to six months and then seven to 12 or something like that because it does sound -- the things that

we've seen, there's something goes on at about six months, and you're going to have to look at them differently, separately.

DR. WARD: Can I make one observation about the lack of correlation between apnea and reflux as measured by pH probe? And that's the chemo reflex, to invoke that takes a tiny volume of assets that may not always be detected during a pH probe study.

And if you look, however, at children with frequent apnea and demonstrated reflux, whether the two have correlated or not, many times acid suppression reduces their global apnea counts, not in every study.

So we may not have the one-to-one correlation, but it may be our tools for measuring that.

DR. FINK: Can I just make a comment? There is a tool that exists, the Tuttle test. If you take diluted hydrochloric acid and stow it in the esophagus and you induce apnea, then you know you have an acid sensitive infant, and it's an old test. I don't think anybody does it anymore, but it does

exist, and it actually has published data that looked at that exact question.

CHAIRPERSON CHESNEY: What concentration do they use?

DR. FINK: Tenth normal.

CHAIRPERSON CHESNEY: Tenth normal?

DR. FINK: Yeah.

DR. HASSALL: The Tuttle test was the predecessor of the 24-hour intraesophageal pH study. The chemo or regal reflex induced by acid reflux was actually only described in cats in a study -- not by anybody called Cats, but in cats, the animals.

(Laughter.)

DR. HASSALL: By Steve -- by Tuckman and Steve, who's the CEO of CHOP (phonetic), Steve.

PARTICIPANT: Alchava (phonetic).

DR. HASSALL: Alchava. Thank you.

By Alchava and Tuckman. This is, you know, in the early '80s. So the Tuttle test actually is not a provocative test. I guess it could be for inducing respiratory disease, but, in fact, to the best of my knowledge, it just was to find pathologic

reflux, and it was filled with problems because a child could cry and they'd get reflux. If you put a lead hand or a non-lead hand on their belly, they would get reflux.

But I'm not aware of provocative studies that try to induce bronchospasm with the Tuttle test or with the Bernstein test, rather.

DR. FINK: It was actually looking at apnea, central apnea induced by it, and I think it may have been Dennis Nielsen when he was in Utah back in the early '80s. I think it was Nielsen who actually did publish that description.

CHAIRPERSON CHESNEY: One of the interesting things that I think we heard from Dr. Gardener and from Dr. Winter is with respect to the respiratory manifestations as an acid related phenomenon is do we want to ask pharmaceutical companies to answer this question for us or is this something that we should do with other funding to determine if there really is a relationship.

And I must say I was pondering that same issue last night.

But, Dr. Murphy and R. Raczkowski, I need some guidance here. I feel like we've spent a lot of time trying to answer whether efficacy studies are needed, but I think it's been very helpful and very important, and I'm not sure how we can go on until we settle that issue.

DR. RACZKOWSKI: Well, I think the discussion has been very helpful, and I don't think we need to spend any more time on Question 1, but are you saying that you feel -- if there is a need -- what I would suggest in terms of answering the subsequent questions is just assume that efficacy studies are necessary in this age group, and how would you go about answering this question for the respiratory and supraesophageal manifestations of these conditions?

CHAIRPERSON CHESNEY: So if we suspend our questions and accept that we're not exactly sure in what population we need efficacy studies, but if there are some identified populations --

DR. RACZKOWSKI: Right, exactly.

CHAIRPERSON CHESNEY: -- for example, maybe the premature population, then we can go on to

Question 2. Is that a fair statement?

DR. RACZKOWSKI: Yes.

CHAIRPERSON CHESNEY: All right. So let's move on to Question 2, which is if we can agree at some future point that efficacy studies are needed in children, is the proposed placebo controlled treatment withdrawal design acceptable?

And several of you have already referred to this, but comments, questions? Dr. Wilfond.

DR. WILFOND: I'll start off with perhaps something I didn't make entirely clear in my presentation. You know, I do think that the notion of having a withdrawal or escape clause is really very valuable in terms of protecting kids from harms.

But I think the challenge, and this is what I didn't say before, is to define exactly what those withdrawal criteria would be. You know, are we talking about the frequency of apnea? Are we talking about recurrence of pneumonia?

I think we have to be very clear on what it is that we are regarding as failure for that withdrawal criteria to work.

CHAIRPERSON CHESNEY: Dr. Nelson.

DR. NELSON: You know, as described, I think, in the template written request, randomized withdrawal study from my perspective looks good. The one questions I have is the extent to which designs sort of move beyond the written request, particularly when it begins to include invasive endpoint measures that are really different than the respiratory or supraesophageal.

IRBs struggle, particularly if they're careful about doing what Ben referred to as the component analysis of risk when you've got invasive endpoint measures that are not normally performed clinically, and if pediatricians or pediatric gastroenterologists are not normally, for example, doing follow-up endoscopies, the argument then that there is direct benefit is felt to be, in fact, false because if there was going to be benefit, you would have been doing follow-up endoscopies at that time anyway.

So the risk assessment of those invasive tests are important.

Absent that in the current design, to the extent it's looking at apnea and bradycardia, which is not using invasive endpoint measurements, I don't see anything difficult with the design, but the written request is somewhat permissive in using languages such as "may" or "might" and the like to where it wouldn't exclude adding an invasive outcome measure, which many IRBs would, in fact, not approve given that it wouldn't be done clinically.

So I guess that's to say I would support the way it's written, but I would even strengthen the writing to say that, in fact, efficacy endpoints that are not necessary ought not to be included in studies where it's, in fact, beside the point of the direct primary outcome measure of that particular study.

CHAIRPERSON CHESNEY: Dr. Gorman and then Dr. Fink, Dr. Santana.

DR. GORMAN: The withdrawal design in this particular entity suffers, in my mind, from several possible failure points. One is maturation. Two is something for the acid related diseases, healing can occur and, therefore, would mask the effect.

In fact, the withdrawal methodology suffers from all the flaws that the crossover design suffers from, and I think those have been well summarized in one of our International Council on Harmonization documents, where they actually define the concerns about crossover studies.

Having said that, the population that gets to the point of the withdrawal study has to be very enriched in the sense that I would like those people to have been demonstrated to have tried alternative therapies prior. I don't want this to be a naive group of individuals, infants who then start on this agent initially, and therefore, I think the determination of the inclusion and exclusion criteria is probably much more important in this particular design; that these people have tried feeding manipulations, allergy manipulations.

Perhaps at least for the acid induced things, renitidine is another alternative prior to being put on the protein pump inhibitors.

CHAIRPERSON CHESNEY: Thank you.

Dr. Fink.

DR. FINK: I would like to reinforce Dr. Gorman's remarks, but also add that I think any written question of the agency would probably be premature prior to pilot feasibility studies of the endpoints being included in the written request having been performed because I think what we're really seeing here is a lack of pilot and feasibility data, and I don't know how you can actually ask for a study to be performed if you don't have some pilot and feasibility data on the proposed endpoints.

Dr. Santana.

DR. SANTANA: Well, just a general comment that I was wondering whether the study design issues might be different in the neonatal population versus the older population in terms of the population at risk and the confounding factors.

I was impressed by the discussion with the neonatologist this morning trying to define the endpoints, how that population is not very homogeneous, whereas I have always thought in a withdrawal type study you really start off with a population that's very similar, very homogeneous, and

then it allows you in this initial period to define the benefit very clearly.

Now, I'm not sure that the neonatology population with all of the risk factors that we've heard this morning, whether that study design would benefit them, that a different, alternative design, standard placebo, up front control trial without the withdrawal phase may be more appropriate for that population because of the endpoints there, whatever you define, if it's apnea or bradycardia, can be observed very quickly in a very short period of time, and you minimize the risk to those patients getting therapy for a long period of time before the actual washout and randomization to the placebo.

So just a comment in terms of study design for the different population in terms of age groups.

CHAIRPERSON CHESNEY: Dr. Wilfond, I'd like to hear your response to that, and then Dr. Blackmon and Dr. Ferry.

DR. WILFOND: I just went to get a cup of coffee and I didn't hear what you said. I apologize.

CHAIRPERSON CHESNEY: I think what Dr. Santana commented on, that the withdrawal design is most applicable to a homogeneous population, and that what we heard from the neonatologist is that this is not necessarily a homogeneous population. Is that --

DR. GORMAN: Well, your withdrawal design issue is that you start with a fairly uniform group, and then at the end of that period, you define the benefit or not benefit, and people get randomized to continue or placebo.

I'm concerned that the neonatology group of patients is so confounded by so many other medical problems that these patients are having that if you allow that prolonged period of initial therapy for everybody, that I think you're actually exposing patients to a drug that is ultimately of no benefit.

And so I want to shorten that period as quickly as possible by not allowing that withdrawal design up front.

CHAIRPERSON CHESNEY: Thank you.

DR. FINK: Well, I think it might be worthwhile to clarify that. As best as I can tell,

there are two components of the design. The first part is the initial run-in period, in which everybody is on the drug.

Additionally there's the issue of during the placebo controlled part of having very specific criteria for withdrawing a period from the study, and I think you could separate those two questions out. So one could envision a placebo withdrawal study in which there was on run-in period and in which you just took people and put them on either active or placebo and then still had your stopping rules.

Although I think that your other question about the heterogeneous populations, I think, is important because you need to be able to identify the types of patients in which the drug was helpful, and if the population was too heterogeneous, it might work in some subgroups and not others.

So I think we would have to be clear about what the right groups were.

CHAIRPERSON CHESNEY: Dr. Blackmon.

DR. BLACKMON: Before Dr. Ward left, he and I explained a couple of ideas that I'd like to put

out that may address this issue.

When you deal with apnea in a pre-term population, it is multi-factorial, and that's one of the problems in trying the design. But, in fact, apnea of prematurity that is maturational in terms of respiratory drive and many reflexes tends to subside in the bulk of pre-term infants at about 36 weeks' corrected gestational age.

And by what we have most recently learned in a very large study, it's virtually gone by about 43 to 44 weeks, corrected gestational age. So that if you designed your group to enter those infants who are symptomatic, and you can define your symptom complex, at 36 weeks corrective gestational age and their exposure to the treatment was within that window between 36 and 44, preferably not that whole time, but some portion of that time, and the randomization to placebo control occurred only in those infants who actually responded by a change in their apnea symptomatology, I think you would then get a very nice study group in which you could say the PPI really did have an effect or did not have an effect.

CHAIRPERSON CHESNEY: Thank you.

Dr. Ferry and then Dr. Nelson.

DR. FERRY: My comment was really related more to the children probably from zero to one year of age or perhaps older, and that has to do with the run-in period itself.

Certainly if you maintain that run-in period I don't know how long, four weeks, six weeks, certainly eight weeks, you're going to produce healing that you'll no longer be able to see a benefit. So the critical piece of that would be, you know, what is a reasonable time to keep patients on the drug. Is that two weeks? And, you know, what is the basis for that? Is it a steady state of the drug? Is it some early symptom relief that then you can see, you know, worsening symptoms again?

It gets to be very tricky, I think, what that actual run-in period would be.

CHAIRPERSON CHESNEY: Dr. Nelson and then Dr. Raczkowski.

DR. NELSON: I guess just one quick comment just in response to that. The esophagitis

would be an efficacy endpoint through that we've already decided would be unnecessary. So it's not clear to me that the issue of healing would necessarily undercut the study, although it raises a question for what the mechanism might be for apnea and bradycardia.

But, you know, my question goes back to Victor's comment about the differences between a standard placebo design and a randomized withdrawal. If there's evidence that acid control decreases apnea and bradycardia, and I guess by not having looked at the neonatal literature for a while on that point, we not only have to -- if there is, we not only have to consider the use of proton pump inhibitors, but the use of renitidine and other agents in deciding whether it an be approved under 5052.

In other words, you have to consider the risks and benefits over the alternatives, which is not just the alternatives in the trial, but the alternatives that that child would or would not receive outside of the trial.

You know, if there is no evidence -- and

part of the discussion is do neonatologists do evidence based medicine or not -- but if there is no evidence, I guess then we could debate that.

But if there is evidence that renitidine is helpful, then I think you would have to design a trial that would basically only enroll infants who failed both the standard positioning, all of the various things that have been discussed about as well as failed renitidine before you then went on to take that population and put them in a proton pump.

Having said that, if that's the population that's already failed all of those therapies, I don't think there would be a problem in designing it as a standard placebo controlled trial. The assumption in designing it as a randomized withdrawal is that acid control is effective.

DR. SPIELBERG: Can I ask Dr. Murphy and the GIT what is the current status of H_2 labeling specifically with respect to newborn?

I know there have been studies done on some of these compounds, but what is the status with respect to current label and data for newborn use?

DR. RACZKOWSKI: Yeah, I think renitidine has labeling all the way down to birth, and I'm not sure about famotidine.

DR. GALLO-TORRES: It goes all the way down to zero to one month.

DR. RACZKOWSKI: Okay. Well, we're sure that renitidine has labeling down to birth.

DR. SPIELBERG: And in that context, is there anything about what we're talking about here today?

DR. RACZKOWSKI: Okay.

DR. SPIELBERG: The use indication.

CHAIRPERSON CHESNEY: And what is the labeling for renitidine?

DR. RACZKOWSKI: Okay. What was requested of renitidine is pharmacokinetic and pharmacodynamic information down to birth. Renitidine does have labeling for treatment of gastroesophageal reflux disease, but that was at a time when the written requests were being written without complete appreciation that the efficacy may not be extrapolatable just on the basis of PK/PD data alone.

And so we've taken a shift in our approach, particularly the powerful proton pump inhibitors, to request efficacy studies in kids less than a year.

I'd like to address a couple of comments, I think, that were made. One has to do with the heterogeneity of the treatment groups, and I agree that if a population could well be defined up front, that would be the ideal way to go.

But there's a couple of things in this trial design that help handle heterogeneity. One is, as has already been discussed, is that when patients are enrolled in the run-in phase, it's the patients who continue to the randomized withdrawal who are the patients who appear to be responding.

So it's an enriched population, and by definition, it's a less heterogenic population. Another way that the heterogeneity is handled is just through simple randomization, and we certainly acknowledge the fact that if you have a heterogeneous population, that will require larger sample sizes to get the same answer than less heterogeneous ones.

But I don't think that the study design per se is an issue with regard to heterogeneity. It's more of a function of can you identify the population that you want to identify to enroll in the trial, and one way of doing that is through the enrichment phase of the randomized withdrawal, which is the run-in.

And I'm not sure I completely understood Dr. Nelson's comment about renitidine. I would just simply say for other blockers, I would just simply say that these written requests are brought out and are not as detailed as a protocol might be, and that use of other agents like H_2 blockers could be written and that sort of thing, and whether they should be excluded up front or whether they should be controlled in some way in the protocol or in the study can be handled in the protocol, not necessarily in the written request.

So those sorts of issues can be handled in another form when we actually review the protocol to exclude confounding factors.

CHAIRPERSON CHESNEY: Could I ask for other comments? Dr. Nelson mentioned a standardized

placebo controlled study as being an alternative if everything else had been tried and was unsuccessful. What would people's response to that be?

Dr. Danford.

DR. DANFORD: It occurs to me that if we insist on trying other methods for a period of time to make sure that the patients are unresponsive to standard methods, as good an idea as that is and as much safeguard as that gives the patients, that does chew up valuable time which will be further consumed in the run-in phase in a condition that sounds to me as though it spontaneously disappears over a fairly short period of time.

And I wonder if we would be losing the opportunity to identify a clinical effect if we were too restrictive in our inclusion criteria to the point where we would be trying all of these other things first.

CHAIRPERSON CHESNEY: Dr. Nelson?

DR. NELSON: I guess I agree with your procedural concerns, but in evaluating as I might, looking at it on an IRB, I would just say, "Well, I

guess sorry about that."

If, in fact, equipoise is required, meaning you can't put a child into a study that places him at a disadvantage against whatever treatment they may otherwise receive, what clinicians are doing or gastroenterologists are doing in taking care of these patients is relevant, and whether they've failed traditional therapy would be relevant to that.

I'm somewhat dependent. I haven't heard a lot of evidence to say we know what we're doing in this very young age group, and if that's the case, equipoise does exist.

But to the extent that we're trying positioning all of those other things at least should have been tried and failed if you're going to do a standard design, enriched design as an add-on; I think would be also the point that was made earlier, is you presumably were adding on PPI to these other standard therapies that I think most pediatricians would provide.

Otherwise, I would argue it's not in compliance with the 5052 and cannot be approved.

CHAIRPERSON CHESNEY: Dr. Wilfond.

DR. WILFOND: It would seem to me that there's an equal amount of skepticism for renitidine, as well as proton pump inhibitors, in terms of the ability to effectively treat apnea and bradycardia. So it's not clear to me that on that issue it's essential to try one way or the other.

But, Skip, the question I had for you is in terms of your talking about more standard placebo control trials, again, I was still unclear whether the part that you were suggestion is not having a run-on period or not having the withdrawal part later on, or both.

DR. RACZKOWSKI: I think you've defined a population that has failed to respond with what would be considered appropriate evidence based interventions and not just whatever we're doing because we think it works.

Then for that population equipoise exists to then make an intervention because you don't have any other intervention that's been shown effective. So that's not an enrichment. That's just saying

you're enrolling infants who have failed other therapy.

Now, I agree there's a problem if development gets better in three months and it takes you two and a half months to fail other therapies, but that's a practical issue that would have to be looked at.

So it's neither an enrichment nor a withdrawal. It would be selecting a population for which you truly in equipoise about -- in other words, they failed therapy that's been shown effective in other settings.

CHAIRPERSON CHESNEY: Dr. Hassall and then Dr. Hudak.

DR. HASSALL: Just a question for my neonatology colleagues. Assuming that we really don't want to treat life threatening events with proton pump inhibitor or renitidine, and let me back up one step.

We do know that some children who have apneas or direct aspiration are dramatically improved by anti-reflux surgery. So I just wanted to ask you: in designing a study like this, how are you

separating out those patients with apneas and bradycardias who may be having apnea and bradycardia due to prematuring, due to aspiration, and how do you in your clinical practices decide what tests to use or clinical appraisals to use in deciding how to send a patient in your unit for an anti-reflux operation?

In other words, what's the spectrum here? And how could you sort out those patients who might actually be benefitted by an operation rather than by an acid reducing drug?

DR. HUDAK: I guess I'll try to take that one. Actually in our unit it's very simple because surgeons won't do surgical anti-reflux procedures for children less than four kilograms, and those aren't the children we're talking about.

They're unwilling to do it. I don't know what your experience is, Lillian, but I mean, for all of the reasons that you went through in terms of the short-term efficacy of anisthen (phonetic) and the difficulty of doing it, surgeons I've worked with in the past ten years have sort of backed away from doing these procedures in children less than four kilos.

I guess I've been to harsh on my neonatologist colleagues. The implicit assumption is that children would come to be eligible for this study only after failing all of the other available therapies.

That is not the issue. Those are the kids that would present for entry into the study. So that should be fairly straightforward.

And generally what happens is these children come into a point somewhere between 32 to 35 weeks corrected gestational age, very close by any other criteria for going home, but still have predominantly two issues, and they usually go along together.

One is this bradycardia. I'm going to get away from apnea because apnea is very difficult to quantitate. The WR talks about obstructive apnea with a complicated system of measuring air flow at the nose or the mouth and usually an abdominal or chest wall sort of impedance indicator so that you can look to see whether or not you've got respiratory movements and airflow, and in point of fact, in a busy unit

outside of, you know, units that are very accustomed to doing research protocols, there's so much artifact you could introduce for malplacement of these equipments that I'd like to get away from apnea.

So what we're looking at is bradycardia, which is clear, which can be, you know, captured on the monitor and analyzed, and desaturation or either of those things requiring some significant nursing intervention. I think those are clear.

But you know, the issue there is that they either have that or they've got, you know, feeding problems. I mean, they don't feed well, and you know, that may be a manifestation of reflux at least in some babies, too.

But those are the babies who present 32 to 35 weeks. They've got, you know, generally these two problems together, and I think the question is if you can document that these children do have acid reflux, which would be a short pH type probe assessment, you can debate how many hours you need on that.

I like the idea in this population a placebo controlled trial rather than a withdrawal, the

more I think about it. I think it would be cleaner, and then you would know, you know. You could look at your endpoints 48 hours later and see whether you have efficacy and repeat a pH probe and see if there's any correlation with decreased acid secretion, decreased acidity, and improvement in symptoms on the medication.

So I really think we're getting to hung up about all of the difficulties of doing this trial. I think it would be, compared to other studies I've done, a relatively straightforward trial to do.

CHAIRPERSON CHESNEY: Dr. James.

DR. JAMES: Dr. Hudak, what I think I hear you saying is that you would disagree with the inclusion criteria for the pneumogram that's currently in the written request. You're advocating more of an inclusion criteria that includes bradycardia and feeding difficulties.

DR. HUDAK: I think lots of babies have obstructive apnea that doesn't result in bradycardia desaturation, and I don't know what that means clinically.