

# Exception from Informed Consent for Pediatric Trials

MCHB Webcast, March 25, 2011

SUSAN McHENRY: Good morning. This is Susan McHenry with the National Highway Traffic Safety Administration Office of EMS. Thank you for joining us for this Pediatric Exception From Informed Consent webcast. We'll be going until approximately 1:30 this afternoon. The slides -- hopefully you're all logged in okay. The slides will appear in the central window and should advance automatically. The slide changes will be synchronized with the speaker's presentation so you don't need to do anything in terms of advancing the slides. You may need to adjust the timing of the slide changes to match the audio by using slide delay control at the top of the messaging window. And we recommend you change the setting to 12 seconds. That seems to work best for most people. I encourage you to be thinking of questions as you hear the presentations. And you can type those into the message window on the lower right side of the interface. Select question for speaker from the dropdown menu and hit send. And we encourage you to include your state or organization in the message so we know where you're participating from. The questions will be relayed to the speakers but we have a lot of information to cover today, so we may not be interrupting them during the presentation. But we will make sure we get as many questions answered as possible when we're finished. If we don't have the opportunity to respond to your questions during the broadcast, we will email you afterwards. So please be thinking of questions as we go through this.

On the left of the interface is the video window and you can adjust the volume -- I think you're just -- you can adjust the volume on that. Those of you who selected the accessibility features when you registered will see text captioning underneath the video window. And at the end of the broadcast, the interface will close automatically and you'll have the opportunity to fill out an online evaluation. We would appreciate it if you would take a couple minutes to do that. Your response will really help us to plan future broadcasts in the series and improve technical support.

It's my pleasure to introduce to you briefly our three speakers today. We're going to be starting off with Dr. Naynesh Kamani, he's Professor of Pediatrics and Chair of the institutional review board at Children's National Medical Center here in Washington, D.C. Second will be Dr. Jim Chamberlain, the Division Chief of Emergency Medicine, also at Children's National Medical Center in D.C. And he was the principal investigator on the pediatric seizure study. Finally, we'll have Dr. Jill Baren, Professor of Emergency Medicine & Pediatrics at the University of Pennsylvania School of Medicine. And she was the human subjects Principal Investigator for the pediatric seizure study. Dr. Kamani, I will turn it over to you to start.

NAYNESH KAMANI: Thank you, Susan. Thank you for allowing me to present at today's webcast. I am Naynesh Kamani and I am the chair of the institutional review board at the institution of the principal investigator for this trial. Can I have the first slide, please?

So what I would like to do today is present the review of this clinical trial from an IRB chair's perspective. And this protocol, the 3969 is the number given to this protocol at RIB entitled the use of Lorazepam for the Treatment of Pediatric Status Epilepticus: A Randomized Double-Blinded Trial of Lorazepam and Diazepam. Now, it's important to note that this was the first clinical trial that was being conducted in children using the exception from informed consent in an emergency research setting using a set of regulations from the FDA listed under 21 code of Federal regulations 50.24. These regulations allow an Exception From Informed Consent from a research subject or legally authorized representative for studies that involve a requirement for an IND or IDE. For studies that enroll human subjects with a life-threatening medical condition which does not have a proven or satisfactory treatment. For research subjects who obviously are unable to give consent for participation and for studies where the research intervention has to be given prior to an informed consent being feasible. Next slide, please.

For studies that allow informed consent exceptions, there are additional requirements in the regulations that protect these very vulnerable population that lacks autonomy but clearly has unmet medical needs and needs to benefit from new therapies and these regulations were obviously enacted in the late 1990s after the emergency medicine community met with the FDA and DHHS and impressed upon them the need to allow Exception From Informed Consent for research studies in emergency settings, because there was a dearth of studies that had been done prior to that time. Now, additional requirements for protecting this vulnerable population include the inclusion

of a community consultation phase with representatives of communities in which research will take place and subjects are drawn from. A public disclosure phase of information that goes out to the community before the start of the study and with the results of the study at the completion of the study. The PI of these trials, PIs of these trials have to commit to make efforts to contact a family member as soon as possible and there always has to be an independent data safety monitoring committee that has to be established to oversee these trials. Next slide, please.

Now, when I was asked to become chair of our IRB at Children's National Medical Center here in Washington, D.C., this was one of the first studies that I got involved with and clearly there was a very steep learning curve because the institutional review boards have several additional responsibilities which they have to carry out when they approve Exception From Informed Consent studies. And these are listed in the slide I will go through them very briefly. And you will note that a number of my colleagues who are presenting today will also address this in some more detail. So first of all, the disease that is being treated has to be a life-threatening condition, as I mentioned earlier, with unproven or unsatisfactory treatment and where collection of valid scientific information and when obtaining informed consent is not feasible. Either due to the nature of the medical condition, due to a time constraint when the patient presents to the emergency department and/or in a situation where there is no way to identify participants. Now, this for our IRB and a number of other IRBs this was a somewhat controversial topic and I will return to it later in my presentation.

Additionally studies have to have a prospect of direct benefit for research participants. It should not be practicable without the waiver of the informed consent. The research plan should define the length of the potential therapeutic window and the investigator has to commit to attempt to contact the legally authorized representative during this window. The IRB has to review and approve informed consent documents and in many cases these informed consent documents are used when advance informed consent is feasible and should allow the participant to opt out of study at an earlier time so that in case they present to the emergency department with the condition that is the subject of the study, they have the ability -- the emergency room staff should know that they've already asked to opt out of the study and should not be enrolled without -- onto the study. Finally, I already talked about the community consultation and public disclosure form of phases of the study. Next slide.

Now, we had a number of challenges that we faced in the IRB. First of all, as I mentioned earlier, this was the first Exception From Informed Consent study that was being conducted in children. The IRB staff, as well as all the IRB members, myself included, had no prior experience with review and approval of these studies. We had to provide additional training to the IRB membership to enable them to review additional procedures that are needed to give approval. We had to have IRB members participate in the meetings that the research team, the PI and the research team had with members of the community. And the community consultation and public disclosure phases of the -- of these types of studies, the definition of these phases is often a challenge and I'll spend a little more time on that. Next slide, please.

Now, community consultation is defined in the regulations as consultation with representatives of the community and there are two definitions that we need to address here. The community is defined as a community in which the research will take place. So this would be the geographic area where the hospital or the study site is located. Now, for most Children's Hospitals, these are tertiary institutions and attachment area is often quite large so it's difficult to define exactly what one means by the geographic area. The other definition of community is the community from which research subjects will be drawn. Now, this is defined as the group of patients or research subjects who share a particular set of characteristics. So in the case of the study that we're discussing today, these would be patients with -- who present to the emergency department with status epilepticus. Now, as we reviewed this study we were obviously told there are two groups of patients that present to the ER. One is a group of patients who have a known seizure disorder and these patients and their parents are obviously easy to target prior to the start of the study like that. Inform them about the study. Ask their permission to allow their children to participate should they present to the ER in status epilepticus and this is the group that we did not have a lot of problem with. But then the second group is a group that presents to the ER for the first time in status epilepticus with no previous history of seizures. This latter group is obviously hard to identify prior to presentation and this is the group where prior informed consent cannot be obtained. And this is where we had our IRB certainly had some problem. This problem came up at a number of our meetings. And the question was brought up why not exclude this group from participation? This would mean that

any patient who presents to the ER for the first time with no prior history of seizures in status should not be included into this study. And we were told by the principal investigator that this would eliminate a significant percentage of children that present with status epilepticus and would introduce a bias into the interpretation of this study. And I know for a fact that there was another IRB in the country where they basically refused to allow the exception for informed consent for this group of patients. So defining the community is a challenge and should be discussed carefully depending on the nature of the study. Next slide, please.

Now, during the process of community consultation and public disclosure components of the study, the IRB request the PI provide us with a draft plan for community consultation and public disclosure. And this meant that all materials that were going to be used during the community consultation, including slide presentations, surveys and other tools, needed to be reviewed by the IRB and approved. Similarly, any literature that was going to be used for the public disclosure piece, radio ads, print ads, etc., needed to be reviewed by the IRB as well. The IRB review required the PI to provide us with quarterly progress reports on the progress of the community consultation phase. During the review process, our IRB requested that the investigator provide communications from other participating sites on their plans for community consultation. This was mostly a request designed to help our IRB assess whether the community consultation was being done adequately and appropriately and whether we had the opportunity to learn from other IRB experiences. We also reviewed and recommended changes to slide presentations that the research team was going to use

for meetings with the community. And we also requested the PI to develop an information sheet for participants and for the community consultation piece so that these could be handed out at meetings and focus groups. Next slide, please.

The IRB review of the community consultation plan, we -- our IRB decided that we were going to ask the PI to present a quarterly review on the progress of their community consultation piece. All activities were summarized by the research team and presented to the IRB. The surveys the research team was conducting with members of the community were summarized and reviewed during our meetings. Any letters or meeting minutes of community advisory board meetings were also submitted for quarterly review and we asked the PI to summarize any community feedback they had received as part of the community consultation piece. As we reviewed these, the IRB members' role was to determine whether the community had been sufficiently consulted about the study and this is a question that I will address briefly in a minute or two and I think other speakers may also address. And does feedback from the community, if any, necessitate revisions to the community consultation or public disclosure plan or the protocol itself. Next slide.

There were a number of challenges during the community consultation piece that I have already alluded to and I'll briefly discuss here. The definition of community as I mentioned earlier is not really clear in the regulations. And when we say the geographic area, does it mean -- does it mean everybody in the community at large? And at least I felt and a number of our IRB members felt that in a study like this, the

community at large really does not seem to be very engaged with the research trial. Does not have a vested interest in the research trial because for the most part they would feel like they are not likely -- their children or their communities are unlikely to be involved in the research because they don't have a child or they don't know of anyone who has a seizure disorder likely to be affected by this. And it was clear from the community consultation piece that our research team conducted that the community that was most engaged with the research team was the community that had already been affected by seizure disorders. So parents of children with known seizure disorders were the ones who were most invested in this trial. And so the definition of community could be broad or it could be as narrow as the population that is seen in the emergency department with seizures or being followed in epilepsy clinics at our institution. The process for conducting community consultation is obviously not specified in the regulations and so different institutions and different research teams may have different approaches as to how they are going to consult with the community. This could include community advisory boards, this could include telephone and paper surveys. It could include in-person meetings or focus groups. Or it could include meetings with leaders of community organizations, as well as leaders of -- from within the community that the institution serves. Next slide.

Now, in the case of our institution, Dr. Chamberlain and his team conducted the following effort as part of the community consultation piece. They had in-person -- several in-person meetings with parents of children who attended neurology -- who had appointments in the neurology clinic. So this obviously included a significant

number of individuals whose children had seizure disorders. They had in-person meetings with parents of children who attended -- who had -- who had presented to the emergency department for seizures, as well as for any other condition. And then they held a number of parent and community meetings in community settings. They also had regular communications with community-based organizations, churches, parent support groups and they also had a community advisory board with whom they met on a regular basis apprised them of the study as well as the progress of the community consultation. And I think Dr. Chamberlain could comment on this more but clearly the challenges that the research team faced was that for the most part, a number of the meetings were very poorly attended and there was a clear lack of participation by non-affected community members. Meaning the vast majority of individuals who attended these meetings were parents of children who already had been diagnosed with seizure disorders and to give you an idea of further idea of the lack of participation, they communicated with a number of parent support groups in the D.C. area and only one out of 17 non-epilepsy community parent groups responded to their request. 0 out of 17 church groups and 0 out of eight other groups responded following contact. So they clearly had a significant challenge ahead of them. Next slide.

The public disclosure piece was -- consisted of brochures, posters and flyers that were posted in the emergency department and neurology clinics. Information about the study was included in The Children's Hospital annual checkup flyer that goes home with roughly 65,000 D.C. school children. Ads were placed in a number of magazines, a number of papers. There was a national website for parents and physicians to go to

to get more information about the study. The 24-hour hotline was created and the print media was provided with information about the website. And a final slide, please. A couple more slides.

The public disclosure had to state that informed consent will not be obtained for most of the patients. It had to give information about the two drugs, their risks and benefits. It had to summarize the research protocol and the study design in lay terms. It had to tell the reader how potential subjects would be identified, what institutions and sites were participating, description of the attempts that the research team would make to contact the legally authorized representatives and suggestions as to how individuals who did not want their children to participate could opt out of the study. Next slide, please.

The questions that arise as the IRB reviews the community consultation piece is when is community consultation or how much community consultation is sufficient prior to IRB approval for the trial to move forward? And in our case, we granted approval to that research team to go ahead with the actual trial after a detailed review of the quarterly summary reports on all activities that had been conducted as part of the community consultation and public disclosure piece, and after the IRB determined that the research team had conducted a good-faith effort and had done due diligence to consult with the community. There is obviously this is not a quantitative -- there are no quantitative goals that need to be met. It is a subjective decision. And certainly there is room for disagreement when a decision like this is made. Next slide, please.

So I would like to end by giving you an idea of how much time it took for the research team to get this protocol approved through our IRB. It was initially submitted in December of 2006 and was discussed at our next IRB meeting in January of 2007. We gave them after a few contingencies we gave them approval to start the community consultation piece in March of 2007. They were then asked to present quarterly reviews of their activities. The public disclosure piece was started in December of 2007 and final approval to go ahead with the actual study and enroll subjects was given in May of 2008. And I believe that the first patient was enrolled in September of 2008. So essentially roughly 21 months between the time this study was submitted to our IRB and the time of enrollment of the first patient. Obviously a very long period compared to most other studies where it usually takes anywhere from three to nine months for this process to be completed. I think I'll end here and hand over to my colleague. Thank you.

JIM CHAMBERLAIN: Okay, thanks, Dr. Kamani. So we should be on slide 17, please. The title slide for my talk. This is Jim Chamberlain from Washington, D.C. and I just want to talk about how we met the requirements for the Exception From Informed Consent in this particular study. So the next slide, 18, is our learning objectives.

I want people to understand what the trial is, understand the justification for using the Exception From Informed Consent and understand where institutions and IRBs might have difficulty with this regulation, with these regulations. Next slide.

The overview of the trial. This is an RCT, double blind trial and we were contracted by the NICHD to perform this trial under the best pharmaceuticals for children act so that we could finally get Lorazepam labeled by the FDA, approved by the FDA for status epilepticus in children. We all use it. It is used in about 80% of emergency departments around the country. But it is not FDA approved yet. The purpose of this study is to get it there. Patients present to the emergency department with status epilepticus lasting -- seizures lasting five minutes or longer. Or having multiple seizures in a row. And the statement of work that we received from NICHD for this study is that we were supposed to administer the drug within five minutes of arrival. We collect efficacy safety data and track adverse events for 30 days. Next slide should be slide 20. Requirements for the EFIC.

So just reviewing briefly again, the regulations, the FDA regulations say you have to have a life-threatening condition, that the informed consent is not feasible within the therapeutic window and the available treatments are unproven or satisfactory. We had challenges with the first and third one. The second one was pretty -- that was a slam dunk pretty easy to prove. Next slide.

How did we prove to the FDA that this was a life-threatening condition? By the way, we were challenged with this study because we not only had to prove this to the FDA and get their approval but we also had to prove this to the 15 different IRBs that we -- at the different institutions enrolling patients. So we know that status epilepticus in

general in children is not life threatening. Most children with status epilepticus do pretty well once you get their seizures under control. The problem is that we don't know which kids are going to respond well and which are not. We don't know what their underlying condition is when they come in. And I think we've all seen or probably most of us have seen cases where treatment occurred maybe a little too aggressively or not aggressively enough and that began a downward spiral of respiratory depression, acidosis, prolonged seizures and prolonged metabolic demand. Perhaps difficulty with intubation and then all sorts of trouble downstream, including cerebral edema, persistent epilepticus and the like. And we actually testified in front of the FDA, Dr. baren and miss that maybe the regulation was a bit restrictive. If we could save neurons or we could save a limb or a testicle, you know, maybe those are worthwhile goals for emergency research as well. But in this particular trial we had to prove life-threatening condition.

The next slide, number 22, talks more about life-threatening condition. We do know that if a child seizes for longer periods of seizures and animals are associated with worsening outcomes and also increasingly -- increasing scientific recognition of the kindling phenomenon. That is, if you get medications on board early, it is easier to stop the seizures and the longer you go, the harder it gets to stop. So the idea that you've got to get drugs on board and in some cases it is going to be life-threatening was enough to convince the FDA. All right. Next slide.

Number 23. So this was pretty easy proving that informed consent was not possible within the therapeutic window. Though we had to get seizure medicine on board within five minutes. That is the generally-recommended time frame for treating status epilepticus. It used to be 30 minutes, then 20, then 15. But now most neurologists would agree based mostly on an may data that if you can get medications on board within five minutes you're more likely to have a successful outcome. Obviously you cannot get informed consent for anything within five minutes. This is particularly true in a case of status epilepticus where the parents may be upset, 50% of parents think their child is dying when they have status epilepticus. So it's not -- this is not a family that you can approach and talk about a research study. It would be impossible logistically and from a feasibility standpoint and I think it would be intrusive and emotionally difficult for the family for you to do so. So we were able to demonstrate to the FDA and the IRBs that informed consent is not possible when in the therapeutic window.

The next slide, number 24, just confirms that. The current recommendation is five minutes. Now, the third condition for the Exception From Informed Consent is to prove that current treatment is unsatisfactory. Well, this is a really vague term. What does unsatisfactory mean? Certainly in CPR where survival with neurologically -- neurologic intact is probably 5%, we would say that current treatment is unsatisfactory but what about status epilepticus? We have die az Pam, which has been labeled -- and it works in 65 or 70% of cases. But what if we have another drug which works in 80% of cases? Then we would consider -- I would consider die az Pam unsatisfactory because it's unsatisfactory compared to the other drug that would provide a more

satisfactory outcome. This regulation is very vague about what satisfactory means and there is a lot of debate about that. The next slide is number 26.

So 80% is probably a good number for adults for the the medications in controlling seizures. In children, there haven't been really good studies but the numbers range anywhere from 65% up through about 81%. So with most -- there has only been four studies in kids. Most of them are in the 70% range. So again, if we can improve that to 75% or 80% without decreasing the safety, then I'm all for that and our current therapy is unsatisfactory in my opinion. And again, we convinced the IRB of that and the FDA. All right, next slide, number 27.

Another thing to look at about current treatment being unsatisfactory is what we know in the past from studies of Lorazepam versus die az Pam. Lorazepam lasts longer, it seems to be more effective in terminating status epilepticus although again, the number studies in kids is small and there has only been four studies. Most of those have been retrospective chart reviews or review after a protocol change, for example. Same with incidents of respiratory depression. We based on some retrospective data know really good prospective trials. We think that Lorazepam might have a lower incidence of respiratory depression. We'll find out at the end of our study but suffice it to say there is insufficient information. We're not sure but we think maybe.

Interestingly Cochran review of this particular issue says there is no good evidence either way to recommend one drug over the other. All right. The next slide is 29.

And again, that kind of summarizes that we don't really have good data on which medication is better. But we think that the current treatment may be unsatisfactory because there is some evidence to suggest that Lorazepam might be a better treatment with fewer side effects. All right, the next slide Dr. Kamani, this is number 33 -- I'm sorry, I've jumped. Hold on a second. I've jumped in my slides. Okay, number 30.

Dr. Kamani mentioned how do you define a community? What we did here at Children's National for this study was we looked at where our patients to the emergency department come from and we looked at those zip codes and reached out to those zip codes and then, of course, we reached out to our seizure families from neurology clinic and from our practices and from the local foundations that deal with epilepsy. Slide 31.

So one of the things Dr. Kamani mentioned is that you have to provide people with an opportunity to opt out. People for various reasons do not want to be involved in research studies for any number of reasons and so the idea of the public disclosure is to be transparent and let everybody know about the study and to give them an opportunity to opt out. So we have a toll free number, a website, and we share the information nationally so that if a family travels and has a seizure in another city in which we're enrolling, it will be on their opt-out list as well. We keep an alphabetical list. Now my last slide is number 32.

And I just wanted to talk about a couple specific institutional concerns that came up. Dr. Kamani was right that there was one IRB that was refusing to allow us to enroll under the exception and would only allow us to pre-consent families from neurology clinic. But, in fact, that institution has reversed its position and is now -- we're now undergoing the community consultation and public disclosure activities to meet the requirements for the exception. So we were able to convince that IRB that we should allow this study to move forward with the exception. And their particular concern was about children. So for some reason there is this -- I don't know what it is, a QUASI ethical concern that we should be able to do it for adults but not for children. Dr. baren and I have had discussions of this and we agree it's not fair to not allow children the benefits of being involved in a research protocol like this. We would never find out the best treatments for kids if we didn't allow children to be in these trials. Public relations were big issues for some institutions. They had previous experience with another Exception From Informed Consent trial that was -- went sour, I would say, and had a little questionable ethics to it so they were nervous about another study in this area. One institution in particular had this concept of community consent. So they read the regulations to say that community consultation meant you had to go out and survey community members and you had to reach 80% approval rate among community members in order to move forward. And that required a fair amount of number of meetings with that IRB to educate them about the idea of community consultation is not about consent, it is about finding out what are the special issues in this community that apply to this protocol and what does this mean for members of our community? And then one institution review board was concerned about delays in

therapy because they thought we might be delaying medications in order to do the randomization, for example. And we actually collected some baseline data to prove to them that that was not the case. So I'll conclude there and turn it over to Dr. Baren.

JILL BAREN: Thank you very much. Good afternoon, everyone. I would like to begin my portion of the talk on slide 33. And to let you know I've been passionately interested in this area of investigation. As co-investigator I was able to bring trials that I did in the adult population to the pediatric population and worked under four different trials under the exception for informed consent. What I hope to share with you this morning are some of the pearls from the planning process for the pediatric seizure study. Next slide, please.

So going back historically at the outset of this study I want everyone to have a little bit of an understanding of how we came to the decision to proceed with the I would say regulatory burden of conducting a trial under Exception From Informed Consent. Our seizure study group had previously performed a farm sue call study looking how Lorazepam performed in children who were in the process of status epilepticus. During that preliminary study which was conducted at about ten sites in our group we identified significant logistical barriers that led us to see how difficult it might be to conduct a secondary randomized control trial under the same therapeutic window constraints. During the preliminary study we had to use a lot of resources to do patient recruitment outside of the emergency department. We had a very slow enrollment process to get to a total of around 60 patients. We had multiple study extensions that

were required all at significant cost to our sponsor and a number of different protocol violations essentially all around the area of not being able to collect particular timed blood samples because of a very prolonged period of obtaining informed consent from emotionally distressed families and children who had presented with status epilepticus. All of that served together for our catalyst for our group to look into these Federal regulations with research without consent. So the pediatric zsh yours study group investigators got together with their expertise made the decision that a randomized control trying to look at the comparison in terms of efficacy and safety between two was not going to be feasible with informed consent. That's the background for how we approached the regulatory aspects of this particular study. Our plan application of 21CFR50.25 acknowledged it was an FD-regulated trial and all criteria had to be satisfied and accepted by the FDA as part of our new drug application as well as all the local IRBs of the participating sites and we also understood immediately that our sponsor would need to inform other investigators at all the different sites that were participating that if for some reason as well as the FDA if for some reason the protocol was not approved by every site in our research group and understood it was a risk at the outset of the study and needed to be tactical and strategic how to carry out our Exception From Informed Consent plan. Next slide, please.

I don't think that we need to review yet again the conditions which make that trial eligible to be conducted under 50.24 so we'll go ahead and skip to the next slide.

Again, both of our previous speakers have identified that there are additional protections associated with these regulations including community consultation, public disclosure that must occur both before and after the trial. The existence of an independent data monitoring committee and the robust process to contact and obtain informed consent from legally authorized representatives. We began our process with a very interesting discussion held at the NIH that involved experts in clinical research. We felt that transparency and honesty and thorough examination of the issues behind conducting such a trial in children would be very important in obtaining buy-in later on down the line. This proved to be quite an important step in our process. After we left from this discussion where we felt that there was generally overwhelming support for going forward with an EFIC trial in children, we advised all of our sites to initiate a very early dialogue with their IRBs in the planning stages of the trial. We actually prepared in a centralized resource fashion an IRB resource finding and also a very detailed centralized operational plan to meet all of those additional human subjects protections that are required for an EFIC trial. For example, at Dr. Chamberlain's site with developed some materials that would go -- that would be presented during the community consultation and public disclosure process and tested the content of those messages on potential end users and we were able to revise those messages based on that community feedback. That was a very nice way to get some material centralized before each site had to develop them. They have a menu of methods that we chose and some of the strengths and weaknesses of the methods in subsequent slides. The same was true for a menu of public disclosure plan. We had an opt out plan that could be presented during the disclosure events in order to feel that the

process for allowing people to exercise their own independent decision making could be carried out in the best fashion and finally we developed a centralized plan and taught sites how to appropriately contact legally-authorized representatives during an enrollment under EIC. In order to define the community for the community consultation/public disclosure process already you heard some of the ways this was done at Children's National Medical Center and I thought I would summarize the general approach here. We asked each site to put thought in describing the area surrounding where the hospitals were that the studies were being conducted. Many of the institutions involved in the study were indeed located in urban areas and serve as referral hospitals increasing their total catch area not just to the neighborhoods adjacent to the hospital but could be considerably far beyond that given helicopter transport and ambulance transport that might occur from suburban and even rural areas beyond. We also considered such things as social influences, regional health services and health profiles of our patients when we put together a profile of what our community was. And in many instances that we found it very helpful to seek assistance from our public affairs offices at our respective institutions or perhaps even the community relations department in hospitals and universities who often have some preestablished connections with communities and could help us to understand exactly which groups really comprise our geographic community. Next slide.

The challenges that we had in this process, many of those you've already heard. Certainly about the large geographic area due to the nature of specialty services provided at academic centers and because of that, we realized that we would instead

perhaps focus much on the disease-based community. Those patients that we could identify that were already afflicted with the condition we were studying, status epilepticus and took into account many other features of the community such as cultural, ethnic and linguistic characteristics. The disease-specific community we were able to help identify by doing a search of emergency department administrative data so in addition to a list of patients that came from neurology clinic who had been previously diagnosed with epilepsy and regularly followed by the hospital, we were also able to capture of population of disease-affected patients who perhaps had utilized the emergency department in the past repeated visits for seizures. So this was a way that we helped to identify and contact the disease-specific community through our community consultation efforts. Next slide.

The community consultation methods that the pediatric seizure study used could fall into four broad categories. The first were in depth qualitative methods predominantly in the form of focus groups, open forums in the form of public meetings, surveys and interviews that were done on an individual basis and then finally, each IRB, of course, had the opportunity to enhance and initiate their on community consultation methods by using specially appointed members and community liaisons. We certainly did not expect our sites to engage in all of those different broad categories of activities. But instead we really favored a customized approach so together the sponsor on a national level, which was NICHD, the site PIs and local IRB, its representatives and site investigators chose activities that they thought were going to be the most feasible, cost effective and which in their best estimation would provide the most adequate

information about the community. So we did not attempt to standardize the amount or the exact type of activities that were recommended for community consultation but rather encouraged this kind of dialogue so that a customized site plan could be put together and given the fact that IRB reviews are often local in nature we do have to pay attention to what the norms and types of populations they serve, we felt this was a very important part of the process. Next slide.

Our public disclosure methods were quite varied in nature. You heard some of them mentioned already. We used public media including newspaper, television and radio and in some cases including foreign language media outlets given the communities that we identified around our participating sites. We capitalized essentially on in-hospital resources by using such things as posters and flyers, newsletters and brochures, etc. And drafted letters to providers and patients themselves essentially announcing the study and what it would entail. And we also took advantage of electronic media. You heard the description of a national website that was developed predominantly geared toward the public and research personnel linked with local websites and in some cases linked to particular foundations, for example the epilepsy foundation would be a predominant foundation involved in our study and had downloadable materials and templates. The opt out form could be downloaded from these electronic media in order to link them to opt out procedures and we made special efforts to have a 24 hour hotline with a recorded message for more detail that allowed those that didn't have access to computerized services to call and leave a voice message if they preferred to opt out of the study being publicized. Next slide.

In terms of our opt-out procedures it's very important for everyone on the call to understand who might be thinking about developing a trial like this that prospective informed consent is the gold standard. And we attempted to perform that whenever possible. We selectively sought out patients and their parents with known seizure disorders and approached them for both consent in various venues prior to the qualifying event, the status epilepticus event for the study. We clearly honored this and that's part of the trial to develop consent materials that one would otherwise do without the EFIC regulations. However, our prior experience in the study that we described showed us we would only reach a few legal -- eligible patients. We set up a website to try to maximize this opportunity to opt out with continuous availability. One of the interesting things that arose in our group in terms of identifying subjects who wished to opt out. There are differences of opinions of how we should attempt to identify those potential subjects. In some cases the local IRB decided together with the investigator that wrist bands would be given to those who did object so they could be easily identified upon potential presentation with status epilepticus. On the other hand, some sites together with their IRBs decided that wrist bands would only be given to those who did provide informed consent. There was a little bit of a difference of opinion on how these patients should be identified. Because of the potential for wrist band to be seen as a stigmatizing type of attire. That was something that went back and forth and was chosen to be handled differently from site to site. Again as Dr. Chamberlain pointed out they ran a continual alphabetical list in the emergency department and some sites linked it to an electronic tracking software in the

emergency department or perhaps even to registration or other clinical procedures.

Next slide.

After enrollment, once a subject was enrolled under the exception from informed concept regulations we sought informed consent to continue in the trial from the legally authorized representative as soon as was feasibly possible. In most cases this would happen after both medical and emotional stability were achieved and very importantly after the clinician was able to have an effective dialogue with the LAR. We sought to have the clinician always introduce the study team member to give us some kind of a sense of when a parent or even a patient themselves were able to be approached following recovery from the seizure activity. At that point we really took the patient through a very detailed consent procedure and certainly opened up the possibility of refusing further study procedures. And if we were unable to find a legally authorized representative quickly after the patient was admitted or even awoke from status epilepticus in the emergency department. We tried to make attempts to contact the LAR -- we performed age appropriate assent through the local IRB. In terms of IRB communications we found it to be an exceedingly critical part of conducting the study and it has remained to be the case of how important communication is since the beginning of the study. So all of our sites as I mentioned had a very early dialogue with their IRBs to structure and plan for their customized community consultation and public disclosures activities. They showed an amazing willingness to work with the investigators. They were often quite serious and excited about how they could operate a trial like this despite the heavy regulatory burden and units of the regulations to many

of their members. What we provided as an investigator group from a centralized national perspective is scheduled education session for IRB members at their sites and we'd go over carefully the requirements of the bill. We provided examples of community consultation and public disclosure activities from other trials that had been conducted and we provided copies to them of the FDA 2006 draft guidance document that talks about how to implement the Exception From Informed Consent regulations and put all these things together in a resource binder which we prepared for them and copied at their request. So that we could make sure that the education for IRB members was maximized. Next slide.

There were some sites in our seizure study network that had prior experience with Exception From Informed Consent and a few sites conducted prior trials under those regulations. Two of those sites had IRBs which actively made recommendations for the investigator with regard with how to conduct the trial and what types of pre-trial activities were needed. There was one site that had a pre-meeting with the IRB to review exactly how the IRB would set out to review a trial like that. So that they got the methodology down pat ahead of time and one site had been so experienced they had a recently approved two studies using FIC so they had an IRB that was already educated about this. Other sites had pre-established IRB policies and instructions for a potential protocol that might fall under 21CFR50.24 but hadn't been challenged with reviewing such a protocol. Some thought about it but hadn't been presented with that situation. Next slide.

What we did was helped craft an overall operational plan for how the IRB should review EFIC and Dr. Kamani talked to you about how that can be quite a different process from the usual review of a protocol not only in time line but also in content. So we in many cases asked for an IRB liaison to be assigned to our site investigator and it was done in several sites and a structural difference for those particular IRBs. The liaisons performed several functions. They reported back to the group on the progress of the trial or any issues that might arise or were available to investigators to speak with them frequently and in many cases the liaisons also attended the community consultation activities and able to give true reports reflecting on what they had observed during those events. In one case there was a special IRB subcommittee or section set up and this was the site that had previously refused to review studies which fell under these regulations and as Dr. Chamberlain mentioned that site reconsidered and chose to allow that investigator to proceed and in several situations in three sites they incorporated the Exception From Informed Consent activities within their existing community advisory board and these are newer requirements for IRBs to actually have on hand and they decided to use that extension of the IRB to do many of their EFIC activities. Next slide, please.

Challenges, many of them have been mentioned, again one IRB persistently used community consultation results as indicative of community consent for the study to take place. They had predetermined a threshold level of agreement. They wanted to see throughout the community consultation activities a level of 80% or greater of individuals that would agree to participate in the seizure study. And we had to do

many different types of education and working with the investigator to try and help that IRB understand that was not indeed the intent of community consultation. Several IRBs also expressed concerns about the identification procedures for patients who wanted to opt out. The differences of opinion in terms of wearing wrist bands and investigators -- we had a debate sometimes about what would be the most appropriate time to lay out the concept of the research that was being done and people had different clinical experiences and brought that into the discussion so certainly these were all challenging things not just between investigators and IRBs but among the investigator group themselves. Next slide.

We already talked about the various definitions of community. I'll just skip over that. In terms of public disclosure, there was a potential we recognized early for enormous expense associated with these activities with potentially little effectiveness. How to get a message across to a large urban community? We realized trying to do that by using television or radio ads alone could cost thousands and thousands of dollars. We struggled with this to a large degree not sure how to get the message across to the interested public and didn't really have a good way or weren't really able to go back to prior literature and understand what were the most effective ways to perform public disclosure. This is still an area, I think, within the regulations that is continuing to be a challenge for most investigators and IRBs. Next slide.

In terms of our progress, each site came up with a specific plan for meeting the EFIC requirements. I mentioned the customized consultation and public disclosure activities

and I think what was very helpful for our group was an executed step wise IRB submission roll out of community consultation. You saw how we summarized that different sites had differential experience. We allowed to more experienced sites to go first and agreed amongst our group it was a great potential to share information with either positive or negative implications. Next slide.

Our study management structure I think was rather unique and worked very well. We developed a co-PI structure at the national level between Dr. Chamberlain and myself. Dr. Chamberlain was the scientific investigator responsible for the detailed protocol development, the IND discussions with the FDA and really planning the very specific methodologies and actual operational policies of the trial. I served in the role as coordinating human subjects investigator and developed and implemented the aspects of the regulatory project and human subject protection. That freed me up to focus on the issues that are very sensitive and important in the trial and able to create an overall plan and it gave our entire investigator group the opportunity to really carefully examine all aspects of the process. Dr. Chamberlain and myself shared joint activities for steering committee leadership, interfacing with the sponsor and the trial preparation and conduct. Let me go through with you just briefly in the next few minutes some of the lessons that we learned from some of our community consultation activities. I would like to focus predominantly on the focus group methodology which we chose to use at our particular site. We conducted four of these at Children's Hospital Philadelphia and found that our participants were generally very much in favor of this research being performed without consent. We were able to identify common themes

that came up with every single group and they focused on concerns about side effects of the medications which help people to very much understand the rationale for the study. Some themes about how would the community be completely aware of the study and how would you community be able to opt out. Fortunately, through the content and the messages that we had developed we were able to diminish many of these concerns after further discussion. We had a focus group that involved exclusively adolescents affected with seizure disorders and they as a group expressed willingness to participate and overall we had 91% of our parents that expressed willingness to enroll their child in the study. There were several parents during our focus group sessions that completed opt out forms for various clinical reasons and most often those had to do with recognizing that the nearest hospital where they would be taken was not a participating study hospital. Next slide.

We analyzed some of the strengths and weaknesses of using focus groups for community consultation. I think this is something to think about in those that might be planning for such a trial. Focus groups are an in-depth qualitative method that generally does generate detailed and rich information and it allows you to have dedicated time to really examine the attitudes of a small group of individuals. So what it does is select for interested parties who are essentially more likely to provide meaningful input and that is what you would like to have in many cases. There is the potential for greater interaction among the participants and generally there is good conversation that gets generated directed by the group participants themselves as opposed to the facilitator. We found the focus groups were provided information for us

that was very high quality and very useful in IRB deliberations. And the diversity of information that we got was more dictated by the composition of the group but in general we found great agreement with the -- great willingness to participate in the study without consent. The cost is probably the greatest drawback. It is generally minimal to moderate in relation to the overall study costs but can be as expensive as \$1,000 per conduct of each group. It depends on the facility, whether or not you provide refreshments, whether or not you will be reimbursing subjects for travel expenses and what you would have to pay for a facilitator. Next slide.

After each of our focus groups, our liaison sent an interim report to the IRB chair and then provided a progress report during full committee meeting and based on the information that was gleaned from our first three or four focus groups we were asked to conduct an additional focus group involving parents and teens without a seizure disorder. Really acknowledging that many times patients that could be enrolled in this trial will be presenting for the first time ever with a seizure. The summaries of the information and the individual transcripts were made available for the IRB deliberations and this was -- led to full protocol approval after these community consultation reviews. Next slide.

Our survey methods was another very highly utilized community consultation method across the study in all the sites and I'll briefly review some of the lessons learned if from that. We approached adult accompanying a child in the emergency department or neurology equipment. No requirement for a complaint related to seizure in the

emergency department. Here we were trying to get more at our population that utilized the emergency department as a site of care and it was a cost effective way to also capture the group that might represent patients with first-time seizures. We linked this process to our opt out procedures or possible prospective informed consent. Next slide.

We had hundreds of surveys completed across our study network and an overall summary of our data revealed 80% of participants felt the study was important and would allow the child to participate. Common themes were raised we saw in the focus group. Concerns about side effects and the consent process and also concerns that the Lorazepam was not approved for children and giving a nod to the overall importance and rational for the study. There was high agreement amongst our survey participants that medical research and experiments in emergency care are important but people expressed their concern about enrolling without consent. And overall, 65% when asked about their general feeling about emergency research without consent felt this type of research was acceptable within their community. If you contrast the 65% and the 80%, you can see that when you give more detail about a particular trial there seems to be a greater amount of agreement and willingness to participate than if you talk about this in more general terms. Next slide.

Surveys we found were a controllable way to disseminate information. A one-on-one technique that allowed for greater interaction between the investigator and participant. It was time consuming because of the hundreds of people we worked with and costly

in terms of how many and what type of personnel you use to conduct surveys. There is also the potential for influence on the part of the survey administrator and the feedback that we got from our IRBs was that this information was of moderate to high quality in terms of informing IRB deliberations. Not quite as useful as the focus group information but considered to be important for the IRBs decision making. Next slide.

So just a few pearls in summary from this portion of the talk. It's important for everyone to understand. Conducting a trial is not a random process. It really does take quite a bit of thought and time. I would certainly point out that you should never make this assumption that IRBs are more educated about the regulations than you might be as an investigator. I would recommend not taking a one size fits all approach it is important to try to centralize and template certain materials that might be used in the pretrial activities, I think one has to always acknowledge that IRBs, investigators and communities are characterized by local customs and practices and customization of these types of things is probably the most important take-home point. There are a huge number of misconceptions about the regulations that one has to correct when you go through the process and always operate under the assumption that your materials might not be getting the right message across and that you may have to go through several iterations to make sure that the people that you are trying to connect with through the community consultation and public disclosure process are hearing what you have to say. Next slide.

Finally, successful strategies that I leave you with. I think certainly developing a plan and strategy for the global administration of the human subject aspect of the trial is very important. People often refer to me as the human subject czar but it is an important role and I think Dr. Chamberlain would agree that this was indeed an important piece to carve out in terms of getting the job done. And I would recommend an early appointment of a data and safety monitoring board to review the EFIC plans that are being put together by the individual sites. This helps up front if a data and safety monitoring board can give some input before this would be submitted to an IRB. I recommend that investigator initiated IRB guidance through the process is essential. Again, just reemphasizing that investigator communication is the corner stone of the process and need to set about a way of correcting this conception about the regulations and finally pilot material and be willing to make changes based on community input. And I'll go ahead and stop there. Thank you very much.

SUSAN McHENRY: Thank you so much to our presenters. That was an awful lot of information on I think an exceptionally well-run trial that paved a new pathway for a lot of us and we really appreciate all the effort that went into this. I would encourage our listeners if you have questions to enter those. In the meantime I have a couple I would like to ask of our panelists. With all the effort you just reviewed with us and all the different methods of community consultation and the full analysis, how do you know when the community consultation and/or the public disclosure has been successful?

>> That's really important to be thinking about that all the time because we don't have unlimited amounts of time and money to get studies completed. There is new information available every day in the scientific community and we want to make sure the question we're asking is answered in the timely and efficient fashion. One of the ways that I think we were able to know when we reached the point where our information wasn't going to change any longer was by utilizing that IRB liaison. Having that person available at our different events mostly focus groups and public meetings. They were able to see for themselves when we would reach saturation. For example, after we conducted the first two focus groups and identified the salient issue the conduct of additional focus groups wasn't providing anything new or different despite varying the participants. I think when you finally start to hear that the issues being identified are the same time and time again I think you know you've completed and maximized your ability to get the information and to understand the issues of the community. I think the same holds true with looking at surveys of individuals. One can see after perhaps looking at 25 or 50 if you're, again, not seeing substantial differences when you vary the participants, then you know you've really gotten the information that the IRB will find useful.

NAYNESH KAMANI: Let me just chime in there, this is Dr. Kamani. I agree with Jill that is one way to make the determination that perhaps the community consultation phase has been completed. What we noticed in our IRB deliberations was we decided we did not have an IRB liaison as Dr. baren has mentioned but we asked several different members of the IRB to represent the IRB at community consultation meetings

which were attended by anywhere from 15 to 25 individuals and we seemed to be getting the same information back and so I actually attended one of these meetings and confirmed for myself that really at this point additional meetings were probably not going to achieve a whole lot more in terms of consultations with the community. Brought that information back to the IRB and it was at that point we decided that once everything -- the whole effort had been reviewed and summarized, that we felt comfortable in going ahead and approving the community consultation process.

>> Okay. Thank you very much. Dr. Chamberlain, what do you see as shall -- what is or is not different to the pediatric population as to the consent and do you think the EDIC should be used with children?

>> Well, the main difference between pediatrics and adults is that the pediatric patient can't consent for their own treatment and basically the parent is providing proxy consent for the child. That being said, I don't think that really enters into the Exception From Informed Consent. The situation is often with an adult that they'll present on their own or they'll present with family members who would also give proxy consent in an emergency situation. I think that given the regulations and their intent and the care with which we carry them out, I think it -- we should include children in these studies. I think it is the only way we're going to determine the optimal treatment for children. I think it's -- I think it's an ethical crime that we allow individual practitioners to choose therapies on an individual basis but we never study it. And I think that the gold

standard to find out which therapy is best is to randomized control trial and children should be allowed to participate in those trials.

SUSAN McHENRY: Excellent. Thank you very much. Dr. Kamani, I think you had a question that you wanted to ask of your other colleagues while they're on the phone.

NAYNESH KAMANI: Right. So this is a question for both Dr. Chamberlain and Baren. As I mentioned during my presentation one of the concerns that our IRB discussed on a couple of occasions and I know was a clear problem with one of the participating IRBs, and I think Dr. Chamberlain mentioned this in his presentation, was the issue of only enrolling patients who had given prior consent, which would mean that you would exclude those patients who presented to the ER with status epilepticus as their first history of seizures. And I know that we consulted with you when this question came up in our IRB and I believe you told us that there would be 35% of patients would be excluded and it would introduce a bias. I know the other IRB that I mentioned, which perhaps was given the same information, felt that well, they could exclude those patients and then do a secondary analysis of some sort. How did that proceed and how did you convince them eventually that that was not a good plan?

>> So yeah, we first did our homework, when you asked us that question back when we were starting, and we found that 35% of our status patients were first-time seizures and in fact they had very different diseases than the patients with chronic epilepsy who didn't take their medications or, you know, had otherwise -- had breakthrough seizures.

So we were convinced from a scientific standpoint that -- and the NIC funding the study was convinced that it would be important to include first-time seizures so as not to bias the science of the study. That we would want to include all types of patients. As far as the one institution that wanted to go that route, we really just kept having meetings with them and trying to convince them of this and finally we broke through and were able to convince them that we should allow first-time seizures to be entered.

>> The other thing that Dr. Baren might want to discuss and how inefficient the process is and how rarely you get a child after being consented.

>> Let me go back to another point you made which has to do with bias and so certainly that would introduce scientific bias as if you look at all comers with a range of etiology for seizure. You want to be the global medication for that condition would apply to the vast majority of people that presented with that condition. I think scientific bias is important but there is also a systematic bias that you would be essentially introducing by eliminating patients who could prospectively benefit from that therapy so I think there is an ethical bias as well by taking that population of incapacitated individuals with an emergency condition and only allowing those to participate that had already, you know, in essence guesswork who was going to have that condition develop and systematically eliminate the rest of them. In terms of, Jim, the second point you mentioned had to do with -- I forgot what you were talking about.

>> The inefficiency—

>> Exactly. In the study that I talked about the preliminary study that we were required by the FDA to do as part of this scope of work, had us looking at serial -- serum levels of Lorazepam to understand the -- it lacked the prospect of direct benefit we were able to demonstrate through a variety of secondary data analysis that approaching thousands of patients and literally this was, you know, somewhere between 1,000 and 2,000 patients approached in clinic settings, on the off chance that they might have status epilepticus event I think we only ended up having three of those patients enter into the trial presenting to the study emergency department. So essentially we went from expending considerable resources to obtain informed consent from over 1,000 patients only to find that maybe three entered the trial in the long run. It was quite an expensive and inefficient endeavor in order to try to get consent in that fashion. That dataset we've used in part to discuss the prakability issue with our IRB.

>> We did focus groups and follow up groups with families who preconsented to enroll and many of them could not agree or disagree to be in the study because it was too abstract. They had a real problem with concept -- what if my child presents with status epilepticus, would I consent now for you to draw blood to test. The families could not get their arms around that concept actually. It was too abstract for them and many people forgot when they showed up later that they had ever agreed to be in the study and we had to go through the whole consent process over again. So despite, I think we reminded them every 90 days by mail and had them send a form back but when

they actually arrived in the ED he had forgotten they were in the study. There is an immediacy concept there that fails with the pre-consent process.

>> While we're on the topic of cost, doctors, how much of the study costs were given to participating institutions for the pre-trial portion? Meaning the community consultation and public disclosure piece?

>> Oh—

>> I know the original budget was \$7500 per site but I can tell you there was a range involved and some sites got away with utilizing less of that money and others that required -- that had customized EFIC plans might have gone much higher than that with regard to paying for advertisements, either television or radio.

>> Some of them went up to \$25,000 or \$30,000.

>> You're talking at least if you're trying to establish a budget to do a trial like this, you know, depending on the other expenses you should, I think, budget at least 20% of the total budget to be directed toward those activities. You might get away with less but as a conservative estimate.

SUSAN McHENRY: Let me ask just one more final question kind of a follow up to that. We've talked about the cost. Dr. Baren, what is the appropriate amount of time to plan for those pre-trial activities?

JILL BAREN: Yep, that's a great question. So constructing the EFIC plan after a range of meetings with interested parties, probably takes between three and six months and then the execution of that plan probably takes, if you're very lucky and it's quite simple and you are organized and have access to community resources that might be done in about a three to six month time frame but really you ought to think of it being more of a nine to 12 month time frame. There are challenges getting folks to show up at events or getting the right forum for presenting your information. So you have to really I would say at the minimum say six months but consider it could be an 18 to 24 month ordeal as Dr. Kamani presented the time line. That's what it took at children's. You have to have a healthy respect for that potential.

>> Our median time was 10 months.

SUSAN McHENRY: Okay. Well, I think we're at the end of our time. I would like to very much thank our speakers for all the tremendous information that you shared with us today. I would like to also thank all the participants for joining us for this and would encourage you to stay on so you can respond to the brief questionnaire on how this worked for you and then also we'll make sure word gets out so you know when the

archived version of this is available so you can go in and enjoy it all again. Thank you so much, everybody. Goodbye.