

Exception From Informed Consent: Lessons From a Consensus Conference

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SUSAN MCHENRY: This is Susan McHenry with the National Highway Traffic Safety Administration office and I will be your moderator today. I'd like to welcome all of you to the "Exception From Informed Consent: Lessons From a Consensus Conference" webcast. And we'll be going until about noon today. And we appreciate your joining us. I would like to run through a little bit of background information and suggestions for you in terms of how to make this a pleasurable experience for you and then I'll very quickly introduce our three speakers for today. First slides will appear in the central window and should advance automatically. These slide changes are synchronized with the speaker's presentations and you don't need to do anything to advance the slides. You may need to adjust the timing of the slide changes to match the audio by using the slide delay at the top of the messaging window. And it is recommended that you change the setting to 12 seconds as that seems to work best for most people. We encourage you to ask the speakers questions at any time during the presentation. Simply type your question in the message window on the lower right side of the interface and select question for speakers from the dropdown menu and hit send. We'd request that you include your state or organization in your message so that we know where you're participating from. The questions will be relayed to the speakers periodically. We will have a question/answer session at the end. If we don't have the

opportunity to respond to your questions during the broadcast, we'll email you afterwards. Again, we encourage you to submit questions at any time during the broadcast. On the left of the interface is the video window. You can adjust the volume of the audio using the volume control slider which you can access by clicking on the loudspeaker icon. Those of you who selected 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. Please take a couple of minutes to fill in the evaluation. It will help improve our technical support.

I'm very pleased to have with us three really tremendous speakers for this morning's session. We'll be starting with Dr. Jill Baren. She is a professor of emergency medicine in pediatrics at the University of Pennsylvania School of Medicine and second we'll have Dr. Michael Sayre. Michael's an emergency physician with the Department of Emergency Medicine at the Ohio State University and we'll be finishing up with my Federal colleague Sara Goldkind. She's a Senior Bioethicist with the Food and Drug Administration and been of invaluable assistance to us in all of these areas. I'll turn it over to Jill to begin the presentation.

JILL BAREN: Thank you very much, Susan. Good morning, everyone. I'm an emergency physician and clinical researcher with a fair amount of experience in the conduct of Exception From Informed Consent studies including the first ever exclusive pediatric study that is operating under these regulations. I'll be speaking to you for the next 10 to 15 minutes from the perspective of an overview of the Exception From

Informed Consent regulations in emergency research. I'm also quite interested in studying in a secondary fashion some of the activities that go along with implementing these regulations and clinical trials. I'll try to expound upon that a little bit as we go through the criteria specifically. So if I could have the next slide, please.

So I think it's worth going through some of the background events and to give the audience an understanding of the climate that actually spurred the creation of the current regulations. Back in the early 90s, there was quite a bit of controversy regarding what was known as deferred consent mechanism. It was also referred to as implied consent or often two-tiered consent that often existed amongst investigators working with IRBs to conduct research in the emergency setting and also a discrepancy in the wording between the FDA and DHHS with regard to conduct such a study. There was an overwhelming recognition that these discrepancies could possibly lead to misunderstandings and misapplications when applied to actual emergency research and this was documented under several circumstances. At the same time, there was an important recognition of the need to advance the science of emergency care and without alternative informed consent procedures, the safety and efficacy of emergency treatments could not be determined and clearly this impacts a number of important disease conditions that needed the science to be advanced in those areas. Next slide, please.

These are some of the important historical events that led up to the final creation of the regulations that we're talking about. The society for academic emergency medicine

formed a coalition of acute resuscitation and critical care researchers. It was an organization that represented many national subspecialty organizations and those interested in research. And together they held a national consensus conference on what to do about the dilemma of conducting research trials and informed consent. They made recommendations and subsequently the FDA developed a proposed rule that was open for two months of public comments. It was addressed and the FDA issued a final rule with Exception From Informed Consent for emergency research. It became harmonized and went into effect in November of 1996. Therefore, we've had regulations governing this type of research for over a decade now. In addition, the FDA has issued a draft guidance document both in 2000 and 2006 which helped to guide investigators through implementation of such a trial and we'll refer to this in a little bit in my talk. The FDA has subsequently held several forums and most recently a public hearing in October of 2006 in which investigate force provided testimony giving support for the existence of these regulations. Next slide, please.

What you see here is the preamble to the FDA final rule entitled 21CFR50.25. It states the IRB is responsible for the review, approval and continuing review of clinical investigation and that they may approve the investigation without requiring that informed consent of all research subjects be obtained. With the concurrence of a licensed physician who is a member of or consultant to the IRB and not otherwise participating in the clinical investigation. And the IRB who sets forth to do this must find and document each of the following. Next slide, please.

They must find that human subjects are in a life-threatening situation. That available treatments for the condition being studied are unproven or unsatisfactory. And that the collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular interventions that must be given within the emergency time frame. Next slide, please.

The guidelines also state that one must recognize that obtaining informed consent is not feasible based on the following conditions. And these are very important criteria to be satisfied when performing human research under these regulations. Subjects must be incapacitated as a result of their medical condition. So for example, a patient who sustains a severe brain injury or a patient who is in hypobulimic shock. It must be -- so we're talking about interventions that are going to occur in a rapid fashion in an emergency condition. And there is no reasonable way to prospectively identify eligible individuals for this participation in such a clinical trial. Next slide, please.

The participation in the research must hold out the prospect of direct benefit and this as you will recognize is very important because the removal of the requirement of prospective informed consent. Subjects are in a life threatening situation that necessitates intervention. It is supported to provide a direct benefit to the individual subjects. This proposed trial must be based on important information that was gleaned from pre-clinical studies. The risks associated with the investigation must be reasonable in relation to what is already known about the medical condition of the potential subjects that might be participants. Or what is known about the risks of

benefit of standard therapy and the risks of benefits of the proposed intervention or activity. Next slide, please.

The clinical investigation could not be carried out without the waiver. This is something also very important to be asked when an investigator thinks about planning such a study. These regulations are not meant to make it easier for the investigator to carry out the study just because informed consent is being waived. The research plan must define the length of the therapeutic window based on current scientific evidence and an investigator must commit to attempting to contact a legally authorized representative within that window of time. If it is feasible within the time window to ask for consent rather than proceeding without informed consent. This entire process must be documented in such that the investigators who have to summarize efforts made to contact the legally authorized representative and make that information available to the IRB at the time of continuing review of the study. The IRB must also review and approve informed consent procedures as well as an informed consent document even though these may not be used upon trial enrollment. The informed consent procedures and document are to be used with subjects or their legally authorized representatives in situations where it is feasible and the IRB must review and approve those procedures and the information to be used when providing an opportunity for a family member to actually object to the subject's participation in the clinical investigation. Next slide, please.

There are some very important additional protections which serve as some of the most important and controversial parts of the current regulations and we'll discuss these next. The first is called community consultation. And this is consultation with representatives of the communities in which the clinical investigation will be conducted and from the community from which the subjects will be drawn. Public disclosure must also happen within the community in which the clinical investigation will be conducted and from which the subjects will be drawn prior to the initiation of the clinical investigation and plans for the investigation and its risks and expected benefits are part of this public disclosure process. You'll see the same requirement is upheld with regard to the disclosure of sufficient information following completion of the clinical investigation in order to apprise the community and the researchers of the study, including the demographic characteristics of the research population and its results. Next slide, please.

These additional protections of the rights and welfare of subjects also include establishment of an independent data monitoring committee and absolute requirement of all trials conducted under EFIC and also the requirement that if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, then the investigator has committed to attempting to contact with the therapeutic window the subject's family member who is not a legally authorized representative and asking up front whether that family member objects to the subject's participation in the clinical investigation. The investigator is responsible for making that information available to the IRB at the time of continuing review. The IRB is

responsible for ensuring that procedures are in place to inform at the earlier possible opportunity each subject that gets enrolled in the trial under the regulations or if that subject remains incapacitated, then a legally authorized representative of that subject or a family member must be informed of the subject's inclusion in the clinical investigation so that that person may possibly discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. Next slide, please.

Continuing along this vein, foregoing informed consent does not mean foregoing disclosure to a subject that he or she has been enrolled. If a family member is told about the clinical investigation and the subject's condition improves, the subject is to be informed as soon as feasible and also on the other extreme if a subject is entered into a clinical investigation with waived consent and that subject dies, then information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible. There is a sense of transparency about the entire process. Community consultation is what investigators find to be one of the most difficult elements from the exception from informed consent regulations to be implementing. I recommend that anyone wanting to do a trial go to the document published in 2006. It provides guidance around the conduct of an exception from informed consent study. In terms of community consultation the guidance document asks the question, what is it intended to do? The answer provided is to ensure that the relevant communities have opportunity for input into the IRB's decision making process before the initiation of the study. It provides an opportunity for a community to both

understand the proposed investigation as well as its risks and benefits and to discuss the investigation more fully. One of the most common misconceptions about the process of community consultation is that it does not equate directly with community consent. Rather, the community consultation process is meant to elicit input from the community with the study and the process but not necessarily to obtain an overwhelming mandate for the conduct of the study. The IRB is the body that makes the final determination as to study approval and uses the information obtained in the community consultation process to do so. Next slide, please.

Many methods have been used in trials conducted under 21 CFR50.24. No proven superior method and few studies that exist in today's literature that evaluate the feasibility, add Cassie or cost effectiveness of various methods of community consultation. Prior experience published suggestions that targeted consultation within a specified time period maybe the most important to obtain important community feedback. Different sites that trials may serve that is multi-cultural and multi-lingual would have more challenges. Therefore, it is recommended that investigators should determine from which, if any of these communities, an IRB might be interested in hearing specific feedback from as it would not be practical, efficient or cost effective to conduct trial activities with every single representative group within a community. Next slide, please.

The definition of public disclosure as elaborated by the FDA draft guidance document calls it a dissemination of information sufficient to allow a reasonable assumption that

communities are aware of the plans for the investigation, its risks and expected benefits and the fact the study will be conducted within the community. It also includes dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study's results. Next slide, please.

Public disclosure materials should always contain a clear statement that informed consent will not be obtained for most subjects to be enrolled in an Exception From Informed Consent study. It should also include information about the test article and use a balanced description of the risks and benefits of studying the article. A synopsis of the research protocol and study design should be translated into lay terms and part of these materials and it should indicate how potential study subjects will be identified. Also all the participating sites and institutions and a full description of the attempts to contact a legally authorized representative as well as important suggestions for community members to opt out of participation in the study if they do not wish to be included. Next slide, please.

Public disclosure is a dynamic process and should continue throughout the study period. It may need to include relevant study updates throughout the conduct of the trial. There are many different public disclosure methods that have been used in previous trials and just as I described with the community consultation process few data are currently in the literature as to cost effectiveness. There is a requirement for public disclosure materials to be submitted to the FDA docket with regard to a study under this section. In summary these are the important key concepts regarding the conduct

of the study under the Exception From Informed Consent regulations for research and special emergency circumstances. There is a very narrow exception to the requirement to obtain perspective informed consent and you'll note that is played out in all the specific criteria that indicate that patients must be in a life threatening condition and also when there is not sufficient time for informed consent to take place.

Community consultation before the study and public disclosure before and after the study are performed as part of these trials. Family members are given a chance to opt out of participation. And notification of the subject in the family occurs all the time when feasible. It is also important to understand that written FDA approval is required for conducting such a study either in the form of an IDE or IND and finally, the IRB is responsible for approving this process in addition to approval of the overall scientific research protocol. Thank you.

MICHAEL SAYRE: Okay. Next slide. It's Michael Sayre, I'm an emergency physician at Ohio state and my interest in this goes back some time ago and I have had the opportunity to conduct several trials using the Exception From Informed Consent. I also served as principal investigator for the EMS research agenda project funded by the National Highway Traffic Safety Administration as well as the Maternal and Child Health Bureau and one component of that was to conduct a conference that we'll talk a little bit about. Next slide.

One of the key things that Dr. bar yen alluded to was controversy in these sorts of studies. The controversy has continued despite the rules today. Driven by a couple of

things. One is that patients believe that we actually know a lot about how to treat them in an emergency. When in fact that might really not be true at all. And secondly, certainly the study is done using an exception from informed consent process provides an opportunity for enterprising news media to create sensational articles. And raise questions about whether this sort of research is ethical. Next slide.

One of the real challenges is to continue to justify the need for this sort of research and a recent article by people documents that for diseases that are relatively easy to do randomized control trials, many studies are done but for conditions where it becomes progressively harder to gain consent and to enroll patients, the number of published randomized control trials drops drastically. For cardiac arrest, for example, there are only six randomized control trials published for every 100,000 deaths. And I'm sure if someone did a similar analysis for other emergency conditions, the results would be much the same. Next slide

. The consensus conference was held in February of 2007 sponsored by the National Highway Traffic Safety Administration, Maternal and Child Health and partly funded for the agency for healthcare research and quality. What we were hoping to do was discuss some of the principles involved in conducting a section from informed consent studies and identify potential solutions to some of the challenges. Next slide.

As Dr. Baren pointed out the IRB has significant responsibility for these studies and I had needs to weigh the risks and benefits of participation and essentially substitute its

judgment for the judgment of the potential subjects and the concept is that by getting input from the community, IRB members will be better informed about how potential subjects would view participation in such a study. And therefore would arrive at a reasonable decision on whether or not it's worthwhile to participate and have the study actually occur. A couple of ways we think it is helpful to make it easier to get that kind of consultation is one, is that the investigator and the IRB leadership need to meet prior to submitting any protocol for formal approval. Sometimes that's necessary in order for the IRB to educate the investigator and sometimes it's essential that the investigator indicates the IRB. And they need to come up with a general plan about how they are going to seek feedback on that protocol and outline a preliminary plan for gaining this community consultation. Another suggestion is that an independent ethics expert could be asked to review the protocol to help decide whether it meets the requirements for Exception From Informed Consent. That may be more valuable, particularly in a large multi-center study where the potential risks and benefits are great. Investigators could also consider including information in the protocol about the health outcomes that could be lost if the study is not actually done. And -- or significantly delayed in order to help justify the need for this investigation to happen.

Next slide.

Typically what seems to occur is that many IRBs divide the process into two pieces. One is that they ask the investigator to submit a formal community consultation and public disclosure plan. The IRB reviews that as well as a preliminary version of the research protocol. It provides feedback on the research protocol and the community

consultation plan and then basically it proves the community consultation public disclosure plan. The investigator then does the community consultation with the assistance of the IRB and does the public disclosure and then once the results of that process are known, the IRB decides whether or not to provide final approval for the overall study. That process can take anywhere from four months to more than a year, depending on the ability of the investigator to complete the various parts of the process and gain IRB approval. One group led by Henry proposed the structure for determining a reasonable balance between the amount of public disclosure and community consultation and the relative risks of the proposed research and IRBs might consider looking at that and using that as guidance to decide what is appropriate for the kind of study being proposed. Next slide.

As Dr. Baren pointed out the purpose of public disclosure is to support transparency for all the parties. What we heard at the consensus conference was the threat of widespread negative publicity will provide a strong deterrent for investigators who are considering conducting what the public would likely believe are unacceptable experiments. And so that may be one of the most important parts of a public disclosure requirement. Another important piece is that it can provide information to the public just to help them increase knowledge about important health issues. The public disclosure ought to try to target the population of interest and if there is an opt-out mechanism, it should offer some way of providing that information back to the investigative team. Another important benefit of public disclosure is that it allows the investigator the opportunity to work with the local news media proactively prior to the

initiation of the study and that can have a major benefit in that it can help prevent a loose cannon effect. In other words, the news media are less likely to write inflammatory, sensational stories if they already know about the research study. As opposed to finding out about it halfway through. So I have found that to be a very effective technique and the news media feel included and typically will offer a more balanced stories in that way. Next slide.

An important point about the community consultation is it's really an iterative process, not an event. So initially what many investigators were doing was holding public meetings and what we have found is that the public meetings typically are not terribly effective. They don't most of the time really reach the target audience. Often are poorly attended and take a lot of effort for little return. So it's probably better to actively seek information from the communities and their known representatives. And that requires a bit of work in that the investigator has to reach out to the prospective community. Emory University provided a good example of that in a head injury study in which they worked to speak with ministers in African-American churches since they knew that African-American men were more likely to be participating in the study and that provided an opportunity to speak to members of that community. The community consultation can also explore potential issues surrounding that proposed trial and elicit concerns and suggestions for making it better. As Dr. BAREN pointed out it is not a voting process. How do you measure whether the community consultation has worked? In the conference in Washington in 2007 we heard from one IRB member who reported their IRB essentially did take a vote of comments and people at the

various meetings and did use that information in an advisory fashion. But better ways to measure this might include asking the investigator to describe how the communities were selected, how were the members engaged, what information was discussed, and did they get any comments back? If they didn't hear anything, then that might mean that they didn't have a controversial study or that they never actually reached any members of the community that would be interested. And then they need to document how they're sharing this information back with the IRB. Next slide.

Another way to measure community consultation is to evaluate the impact. So how many people participated might be a measure. How many comments were received, and again, was the feedback constructive and useful and the IRB can use that to see if the community consultation process is effective. Next slide.

Another way to measure community consultation which is more challenging is to evaluate the outcome of that consultation. So conducting some sort of survey or other tool to document improved understanding between communities and investigators. And also to document whether they actually changed something. So if concerns were raised and the protocol was altered, that would be good evidence that the community consultation process was effective. Next slide.

So another key issue that Dr. Baren pointed out was one about consent. One of the challenges here is sometimes the study might have a therapeutic window that could stretch on for several hours and so it might be possible in some cases to contact a

legally authorized representative and other times that legally authorized representative might not be available in a few hours. Sometimes this is easy because the therapeutic window is really short and a few minutes in the case of a cardiac arrest or severe hemorrhage shock and it will never be possible to contact a legally authorized representative and gain informed consent. But in other conditions such as acute stroke or head injury, this window might be an hour or two. A couple of the challenges that are faced is that consent cannot be obtained solely by telephone and this is true for studies conducted under the current Exception From Informed Consent rules. However, written documents can be sent via email or fax to the legally authorized representative so they can review them and then a conversation can happen between the investigator and that legally authorized representative in order to gain consent.

An example of this approach was used in Los Angeles during a pre-hospital study of magnesium for acute stroke. So the paramedics provided the legally authorized representative and the patient with the written information about the study while they were still at the patient's house. The paramedics then called a study investigator on cell phone and the patient and family were able to ask the investigator questions about the study and decide whether or not to participate. And then once the patient reached the hospital, they completed final documentation of the informed consent that they had already provided over the phone. So the actual consent process involved telephones but the written information was still available to be reviewed. That's been written up and might be useful for other investigators depending on the nature of the study. Next slide.

As Dr. Baren pointed out, pre-clinical and animal research can help estimate the rate of decline in a study article's effectiveness. One of the challenges is that over time the benefits may decrease but the risks might remain relatively constant. And therefore, the IRB and the investigator can decide how long they need to wait before they essentially say they haven't been able to get ahold of the legally authorized representative and move ahead with enrolling the subject using the Exception From Informed Consent. And that really should be part of the protocol and documented ahead of time. Next slide.

One of the real challenges is notifying the family and/or legally authorized representative about the study. So in my experience and the experience of others at the consensus conference, this can really vary considerably. So if there are active study procedures ongoing, then the family or legally authorized representative need to give permission to continue the subject in the study and typically that will happen within a few hours and most of the time the individuals are -- involved are very engaged and interested and do provide good information back to the investigator about whether or not that subject would really want to be in the study. However, if the study is over, one of the challenges is to make a judgment about the least intrusive means of informing the family of the subject's participation. And for example, particularly if the subject has died, and at that time it would seem rather challenging to have an investigator basically call the family up the next morning and say just want to let you know your loved one was in a research study. And we're finished with the study but we wanted to tell you

about it. So I think the IRB really needs to balance the various interests involved and determine what best protects the interests of the subject and also at the same time being mindful that regulations state the notification should happen at the earliest feasible opportunity. There is no bright line here. It can be difficult to make sure that all the various needs are actually met effectively. But there are ways to do it. Next slide.

One of the other challenges is to provide subjects with an opportunity to opt out. The rules don't require that potential subjects be given the opportunity to opt out. However, most research conducted using Exception From Informed Consent have provided a mechanism for that. And the rules do acknowledge that this is an option and discuss how the scope of public disclosure should be commensurate with the likelihood of objection. So in the resuscitation outcome consortium studies the investigators reported that as of three years ago, a little more than 1,000 people across North America had opted out of these studies. I would imagine that number might be a little bit higher today. But in those studies, subjects -- people who wished to opt out were provided a bracelet that they could wear so that if they were found in cardiac arrest or with major injury the paramedics would be able to identify them and know they did not wish to be enrolled. There is very limited research, however, on what are the most effective ways to provide information back to subjects who wish to opt out, as well as to the paramedics to identify those subjects. Next slide.

Another mechanism is subjects can object at the time of enrollment. So certainly if the individual is aware that a study is ongoing and expresses objection, those objections should be honored. It, however, is a challenge because there really is sometimes not sufficient time to provide truly informed consent and the IRB needs to weigh the value of providing incomplete information at the time of the emergency and decide whether that really protects the subject's rights versus the integrity of the trial. Next slide.

Another real challenge that came up at the consensus conference was the issue of subjects who discontinue further participation after they've already been enrolled. So this can take several forms. One is that the subject may have already completed all of the intervention and only remaining job in essence is to continue to follow the subject to see if they develop any adverse effects or survive the intervention. Our understanding is that the FDA would basically insist that data collected on study subjects up to the time of the withdrawal must remain in the trial database and not be purged just because the subject declined further participation. While at the same time it's not appropriate to continue to collect data after they decline further participation, at least we know something about what happened up until that time and that information can help inform evaluation of the study article to decide if it really is effective or not. Other countries take different positions on this issue and I think this is one that remains a little bit controversial. Next slide.

So in conclusion, certainly conducting this research using the Exception From Informed Consent rules is challenging. And the lack of this research, there is a real impediment to developing better treatments. But we really do need high-quality research to test the effectiveness of treatments for emergency and life-threatening conditions. Thanks very much.

SARA GOLDKIND: This is Dr. Sara Goldkind. I'm in the Office of the commissioner in the Food and Drug Administration. My experience with research conducted in the emergency setting under 50.24 has dated back to the time that I came to the agency. I have been very involved in providing ethics consultations on specific submissions to the agency under 50.24 and have also been involved in the interpretation and development of policy regarding emergency research under 50.24. And in conducting public workshops to try and gain further input from the -- our stakeholders, investigators, sponsors, and community members, including advocacy groups, as to concerns about the implementation of research under 50.24. Next slide.

What I would like to focus on today is several different key points that will give you a window, perhaps, into understanding how the FDA looks at these submissions and over the next several slides what I wanted to focus on are study design considerations. First and foremost, I want to emphasize that several questions should occur to an investigator or sponsor prior to designing a study under 50.24. And the first is what is the scientific necessity of including subjects who cannot provide informed consent? Are subjects who have undergone some sort of an acute event different physiologically

than those who can provide informed consent? Would studying that population provide more scientifically valid information? And how does studying that population affect the generalized ability of the research result. Another question is can risks be minimized by studying a less sick population? Of course that still has to be balanced against the other issues that I just laid out. And the protocol must contain a justification for conducting the study in subjects who cannot provide informed consent. It also needs to provide a clear articulation of why the therapeutic window was selected and what is the evidence for that therapeutic window? I would again emphasize that all these issues, as well as a sense of -- a projected sense of where you want to be at the end of the research be considered up front so that you can include biomarkers and other measurements in the protocol from the get-go. That information can be part of the informed consent document, can be part of the public disclosure and community consultation materials. Next slide.

You've already heard mention by Dr. Baren that the subjects need to be in a life-threatening situation. I'm not going to belabor that point but I do want to emphasize that a life-threatening situation need not be an immediate life-threatening event that immediately results in death. We understand death to be likely unless the course of disease is interrupted and an intervention occurs prior to the ability to obtain consent. However, we also recognize that an emergent situation is not one that results in a long-term or permanent disability per se such as a permanent vegetative state. And you've also heard Dr. Baren talk about available treatments or unproven or unsatisfactory. And I would like to emphasize here that we think that unproven means

that there is a lack of substantial evidence that a treatment is effective for the condition of interest. And unsatisfactory means that there are drawbacks to the treatment. They can be safety concerns, that there is a poor survival rate, that the treatment is only partially effective, or it takes too long for onset of activity or the treatment has serious limitations in the setting in which it is needed. For example, it might be an I.V. administration when you want to administer it in the field and an I.M. product would be much more easily administered and save time in the field when there are other necessary interventions that must occur. And you also heard Dr. Baren mention the intervention must hold out the prospect of direct benefit. Next slide.

So I would like to emphasize, when you've heard both Dr. Sayre and Baren talked about direct benefit. It needs to be evidence-based. We suggest that evidence can come from other appropriate animal models, from pre-clinical studies, from clinical studies and other populations, perhaps, consenting populations, and all of that information can be used to help inform the prospect of direct benefit. I will underscore, as I do in a later slide as well, that for a study to be considered appropriate under 50.24, one of the key components is that the study-related intervention, not the study itself, but the study-related intervention holds out the prospect of direct benefit. Next slide.

There has been considerable confusion about endpoints that are acceptable for 50.24 studies. I think it's widely understood that mortality endpoints are acceptable but we also believe that morbidity endpoints may be acceptable in the circumstances where

severe morbidity is clinically relevant and closely associated with mortality. For example, the study of stroke, which can lead to permanent disability or death. The study -- you might have a study to improve the treatment of status epilepticus where and appropriate intervention is reduce the time to seizure control. Next slide.

It is incredibly important for all of this information to be well-articulated and justified in the protocol submission, as well what needs to be included in the protocol is a rationale for the selected study design. An active control trial, a non-inferiority trial or placebo control trial all may be acceptable under 50.24. As I mentioned earlier, it's important for us to understand that there is a clinical equipoise between the two studies if you have a non-inferiority trial. That may be acceptable when a placebo-control trial would be considered unethical or whether the currently available therapy is known to be effective but has a serious safety concern. With placebo-control trials we generally understand them to be an add-on trial where you are adding placebo onto whatever the standard of care might be. There are exceptions to this rule. But those would be considered on a case by case basis at the review division level. Next slide.

And there has also been a considerable amount of confusion about whether only phase three trials are acceptable under 50.24. We do not focus on the phase of a trial when we consider its acceptable under 50.24. We focus, as I mentioned, on whether the study intervention holds out the prospect of direct benefit. However, having said that, we generally would believe that PK studies would be done in consenting subjects

and most phase two control trials would be done on consenting subjects where you're looking at dose ranging or safety issues or a biomarker analyses. Next slide.

FDA recognizes that these are very challenging studies and would like to be of assistance, and so with that in mind, we encourage investigators and sponsors to come to the FDA review divisions for what is called pre-IND or pre-IDE meetings where you would have the opportunity to discuss both scientific and ethical considerations related to the protocol submission. Next slide.

Over the next few slides, I want to talk about when you might need an IND or IDE. With a 50.24 study. And the first question, of course, relates to whether or not the study is FDA regulated. Again, one of the confusions that seems to exist currently is whether or not you might need an IND for a randomized study where the random -- the protocol governs randomization of two arms, both of which contain the study intervention of an FDA-approved product that is being used according to label. There are a lot of nuances to this but we believe that the notion of -- exemption is being made as part of the protocol-driven intervention and the randomization scheme. Having said this, an IND is needed for every clinical investigation involving a drug or biologic that is going to be conducted under 50.24. It is not only do you need to have an IND, but you need to have a separate IND, even if an IND already exists for that product. And that is because we want to give special attention to these submissions. We therefore want it flagged with a separate IND. Next slide.

Additionally it should be pointed out that you need to have FDA permission to proceed with a study that is being conducted under 50.24. This is in contrast to clinical investigations not involving the exception from informed consent where the IND goes into effect 30 days after the FDA receives submission. For FDA-regulated products where you have a clinical investigation being conducted under 50.24, you need to have a written authorization from FDA before you made proceed. Next slide.

So continuing the conversation about drugs or biologics. After FDA -- the IND is submitted, FDA reviews the study protocol under the applicable IND regulations part 312 as well as 50.24. I want to emphasize here that FDA has received about 77 submissions since 1996 when the rule came into effect. About 44 of them have been granted approval to go forward under 50.24. This does not mean that all 44 studies have been conducted. The IRBs need to approve the studies and the sponsors and investigators need to actually conduct them. But from FDA's perspective, 44 have been granted approval to go forward. The discrepancy between the 77 and 44 relates to inability to satisfy one set or both of our regulations. There might be deficits in the protocol submission that relate to 50.24, for example, there may not have been an informed consent document included in the packet. Or there might be a deficit in the protocol under 312, the CMC data was lacking, there was no statistical plan for a non-inferiority study or other such issues. And then we would encourage you to communicate with the FDA review division if you have specific questions about your protocol submission even after you've already had a pre-IND or pre-IDE meeting. Next slide.

Now, when is an IDE needed for a study conducted under 50.24 is a little more subtle and a more complicated matter. But I think for the sake of simplicity you should assume you always need to have an IDE for the conduct of a 50.24 study. Again, it needs to be a separate IDE that cannot just simply be submitted to an IDE file. And the reason I say -- next slide -- that it's almost always the case that you need an IDE is because there are some limited exceptions as to in relation to whether or not the study meets the criteria of the abbreviated requirements or whether the device has already been cleared and approved for marketing and used in accordance with its cleared or approved labeling. In those limited circumstances I would highly encourage you to communicate with CDRH and the appropriate review division. But as a general matter, assume that you need to have either an IND or an IDE for any 50.24 study. Next slide.

So I want to emphasize that sponsors, in addition to the responsibilities that they have that are identified under 312 and 812, have additional responsibilities for a study conducted under 50.24. And sponsors must submit public disclosure materials to the FDA docket prior to initiating the clinical investigation. And subsequent to the completion of the clinical investigation, they need to apprise the community and researchers of the study and they must submit those materials to the FDA docket as well. In addition, as you've heard mentioned, FDA requires that an informed consent procedures and document be drafted for all 50.24 clinical investigations in accordance with our 50.25 regulations on informed consent. And this is for a number of reasons. One of which is in the event that a subject would be able to provide informed consent

or a legally authorized representative would be able to provide informed consent. But also such that the information that would be relayed to a subject or an LAR after enrollment would be contained in the document and organized according to the IRB-approved informed consent materials. We also have had concerns expressed to FDA that subjects or their legally authorized representatives or family members are not being notified after research enrollment in an appropriate period of time. That there has been a lapse in between enrollment and notification of research enrollment. And that has been to the Chagrin of family members. I think there was discussion of this issue but I wanted to emphasize that our feedback, all be it limited, has been that family members would prefer knowing earlier rather than having a month or two go by before they're told. So I think there needs to be careful consideration of what it means to -- to take into account potential distress of family members because they might very well be potentially distressed more so from not being notified about something that happened to a family member rather than being told in the acute setting about research enrollment. Next slide.

So what information must a sponsor submit to FDA for a study conducted under 50.24? And over the next two slides I have a list of information for you. As I've mentioned to you, there needs to be very careful delineation of the rationale for the study as well as the study design and the subject inclusion criteria and exclusion criteria, the informed consent document, as well as the plans for community consultation and for public disclosure. Next slide.

The justifications that I mentioned to you about inclusion of subjects who cannot consent, why the investigational intervention may be better than existing available treatments, what information is available that lets you know that the available treatments are unproven or unsatisfactory. What the rationale is for selecting the therapeutic window and a description of the investigator's commitment to attempting to contact a legally authorized representative for each subject within that therapeutic window. Next slide.

I want you to know again, as I mentioned earlier, FDA is available to help you with these complicated protocol designs and submissions and I have provided you with the most up to date information regarding accessing FDA. If you do not know whether you need an IND or an IDE, whether this is an FDA-regulated product or study, whether -- which review division might be -- have jurisdiction over this protocol, then I have provided you with other contact information that should be helpful to you. Thank you.

>> Thank you so much to all of our speakers. Very excellent information. I would like to remind folks that we would love to receive some questions from you if you can type those into that section on your screen. And we'll do the best we can to address the questions that you might submit. And while you are working on that, let me just ask a couple questions of our presenters. let me start with Dr. BAREN. How should an investigator determine which communities to consult with when preparing to conduct a trial under 50.24?

>> That's a really important question. As I mentioned in my slides, the first place to start is look at the community in which you will conduct the trial and the community

from which the subjects will be drawn. Those are explicit criteria from the regulations themselves. It requires a careful review of your patient population, both geographically speaking and with reference to the disease state that you may be studying. And I think it's best to arrange a meeting with IRB representatives, whether it be the executive director, the chair of your IRB or an interested member to vet out what your selection of community members would be. This would be helpful in getting an opinion up front so that when you begin to submit your materials for proposing to conduct a study and you choose your communities they will already have been preselected or specified by the IRB as important communities to contact. So I can give a practical example of that in a current study of pediatric status epilepticus, when we looked at the various communities to select, we chose individuals who were already extensively afflicted with the disorder. And we organized meetings and focus groups with family members that we drew upon from a variety of venues, both the emergency department and neurology clinic at our particular site. But certainly we also recognize that there were -- there was the possibility of recruitment of individuals that had a new onset seizure disorder that might be transported to the hospital by EMS or transferred in from an outlying area from community hospitals. So we chose a variety of communities to have these consultation activities with and again I want to stress it was based both on geographic considerations as well as those that are affected by the disease state that we were studying.

>> Great, thank you so much. Dr. Sayre, let me ask you a follow-up to that. How much public disclosure do you believe is enough for these types of studies?

>> That's a real challenging question to answer. Some investigators have tried to figure that out. And so I suppose there are a variety of ways to look at the question. Obviously it would be ideal if every member of the potential community knew about the study ahead of time, but given how hard that would be to actually accomplish, usually that's not feasible. So it might be possible if it was a very limited population and you could identify ahead of time who they were. But in that case you could also get prospective informed consent. Basically it would generally be exceedingly expensive to make sure that every member of a city, for example, knew about a potential study. I think that really relying on the news media to get the word out to interested people is important. And by ensuring that the information is out there, what's most likely to happen is if there really is something controversial about the study advocates for the community of interest are likely to have a Google search or some other method of identifying these kinds of things and be able to respond accordingly.

>> Okay. Thank you very much. We have a question that has come in from one of our listeners. I would like to share it with you. I think FDA, I think Sara would probably be the best to answer this. In the event of a large-scale nuclear event, accidental or intentional. How would informed consent or medical intervention be expedited or facilitated by FDA?

>> Well, that's a very good question. And it's worth making the distinction between research conducted in the disaster setting and research conducted in the emergency setting. And although research conducted in the disaster setting is a form of emergency research, it is something that we think about with other special considerations, not only research that is done under 50.24. And by that I mean the

Federal government is giving a lot of consideration to how to go ahead and design protocols, have them reviewed and approved prior to a disaster occurring. So that they are ready to be implemented. Some of those protocols may include informed consent and some of the protocols may in effect not be able to be conducted with informed consent. And if those circumstances would preclude the ability to obtain informed consent, then the research would have to meet the other criteria of 50.24. I hope that answers the question. If it doesn't, please feel free to submit a follow-up.

>> Thank you very much, doctor. I know unusual circumstances and we should all be giving some thought to that because we need to prepare for them. Let me ask another question while we're waiting to see if our listeners have another question. Again for Sara. All the studies we've been talking about this morning involve the Exception From Informed Consent requirements. Why must an informed consent document be prepared?

>> We think that it's very important that an informed consent document be prepared and processes be described for obtaining informed consent and the protocol for a number of reasons. Some of which we've already mentioned in our formal presentations. But one important reason is because we don't take it lightly, as you can tell from all the additional protections that need -- and the restricted nature of the use of this regulation, that need to be part of 50.24. And we want to emphasize that, where possible, where informed consent would be possible, then it should be obtained. And therefore you need to have an IRB reviewed and approved document and process. We also think that it's invaluable to have an informed consent document for use when obtaining informed consent at the time that a subject or an LAR is available, but also

as a guide to providing information even if informed consent would not have been able to be obtained.

>> Okay. Thank you very much. Dr. BAREN, when we're talking about the Exception From Informed Consent regulations does it differ for research conducted under the informed consent regulation versus normal research?

>> Yes, it does differ from standard research. Not under these regulations. I think Dr. Sayre pointed out that it is sometimes the investigator who must guide and teach the IRB what is indeed the appropriate way to review the protocol. So I think I mentioned in my slides that not only does the IRB have responsibility to review the scientific protocol and judge the study based on those merits, but has the responsibility to look at the plan that has been set forth by the investigators to meet all of the criteria to be conducted under 50.24 as well as a plan for how to operationalize, implement and gather the information with regard to additional protections. So one of the ways that we have found it to be most helpful in rolling out a study with the IRB together is to arrange to have a pre-submission meeting where the investigator group discusses with the IRB representatives again what kind of communities would need to be consulted with, what would be a good plan for public disclosure, whether or not there will be any concerns with regard to the scientific protocol in terms of meeting the criteria for 50.24. That's also very helpful before one sets about preparing materials which can be very, very time consuming and costly. So the pre-submission meeting is important and what's also very important is the cover letter that helps to guide the IRB through the process so that it's an understanding on their part that they would be reviewing the protocol in the context of 50.24 and granting permission for the investigator group to

conduct the pre-trial activities followed by an aggregate data presented back to the IRB from the public disclosure process so the IRB can use that information in its deliberations. And I think it's also important to remain flexible, to be receptive to ideas that the IRB may put forth and we have also been successful in asking IRBs to provide us with a liaison individual who is dedicated to the trial and perhaps even coming and supervising and listening in and being able to report in person back to the other members of the IRB and found it helpful to provide an IRB resource binder which contains many articles that have been published on the array of experiences with communication and public disclosure, some of which Dr. Sayre referred to in his presentation and also the FDA draft guidance document, as well as the actual code of Federal regulations which outline explicitly all the criteria that must be followed. Taking a number of those steps can be very, very helpful in terms of guiding the review process.

>> Can I add to that, Susan?

>> Absolutely.

>> One of the things that I wanted to emphasize here is that although FDA -- 50.24 nor our guidance mandates that the IRB review has to occur after FDA review, we recommend that actually the IRB submission occur after FDA's input has already been obtained and that's because we may have some significant modifications to the protocol or other supporting documents. And not infrequently these trials are multi-center and so it's easiest and most efficient to have one set of documents that go through either multiple IRBs or to the central IRB and on to the local institutions. So that's our suggestion.

>> Okay, thank you very much. That's very helpful. I think with all these types of issues that whole early communication and coordination with all the responsible parties really helps to avoid confusion and discrepancies so I think that's really good advice from both of you. Thank you so much. Dr. Sayre, let me ask you another question. We talked about life-threatening situations. What is a life-threatening situation mean? If the risk of death is 95% that's clearly life threatening. But what if the risk of death is 30% or 50%?

>> That's a great question. I believe Dr. Goldfind pointed out some of the issues in this regard and sometimes the immediate risk of death might not be very high, say, for example, for acute stroke research, but there is significant risk of morbidity and/or delayed death that could result from the condition. So I think it's clear that these kinds of studies can be done when the mortality rate during the acute period is low, less than 20% or even lower. As long as there is significant morbidity associated with the condition. So I do think that it really will vary considerably depending on the disease being looked at, as well as proposed intervention and how risky that intervention might be.

>> Okay. Thank you very much. I think that helps to clarify things some. Let me ask Dr. Goldfind one more question. Why must the -- must the opt-out mechanism be provided?

>> Thank you, Susan. That is a point of tremendous confusion. Our 50.24 regulation doesn't require than an opt-out mechanism. An ability to wear a bracelet or carry a wallet card or other mechanism be provided to a community prior to initiation of the study so that folks can be exempted from the research should they sustain the injury or

the event that would be under study. However, we give discretion to IRBs to determine whether they think that an opt-out mechanism would be ethically appropriate and practically feasible. And so you may find that an opt-out mechanism is part of a 50.24 research project. I know that one study had bracelets that people could wear to prevent them from being enrolled in the study. Now, there is confusion, however, about an opt-out mechanism versus the ability to withdraw from research. There is always the ability to withdraw from research should the subject of the legally authorized representative or family member don't want that person to remain in the research protocol. That occurs after they've already been enrolled, the ability to withdraw. The opt-out provision occurs prior to enrollment in the research, prior to receiving the study-related intervention. You can have a rather complex set of circumstances if it's a multi-site trial where, with multiple IRBs reviewing the same protocol where some IRBs for some communities may determine that an opt-out mechanism is appropriate, where other IRBs reviewing the same protocol may decide that it's not appropriate and not have it. But we do think that if there is an opt-out mechanism, it should be -- that information should be included in the public disclosure materials and in the community consultation materials.

>> Okay. Thank you very much. We just have a few minutes left. I don't see any other questions from the audience at this point. I just would like to ask each of our three speakers if they have a final comment they would like to make before we wrap up today's session.

>> Sure, I guess this is Dr. BAREN. I guess I would encourage those members of the audience on phone who are interested in conducting trials like this is to really use

some networking ability to contact individuals who have already gone through the process. I think in the decade and a half since the regulations have been broadly accepted, there has been an increasing number of trials each year that are exploring the option of being conducted under a 50.24. And there is a growing group of investigators and a community -- a scientific community around this type of work and so I would ask people who are interested to try and obtain some connections in that regard. It saves an awful lot of work and it really is helpful to draw upon the experience of those who have already been through it. So I certainly would be happy to make my contact information available following this webcast in order for individuals to do so.

>> And I would just emphasize what I mentioned repeatedly, hopefully, in my presentation, which is that the FDA is here to be of help and please feel free to access us.

>> And Michael Sayre, I would emphasize again the need for this kind of research to be done. There are -- there is a lot to learn about how better to take care of both children and adults who do have emergency conditions and we need to get more of this sort of research completed.

>> Okay. We have one final question, I think, that has come in. Comment first that it's been an excellent presentation. And what is interesting is if research plans to use materials or fluids which have been approved 30 years ago but are not tested as giving the usual amount versus minimal amounts that research will require an IND, however, if research would focus on methods of CPR it would require an IND/IED, would you comment?

>> Let me take the manual CPR piece first. If you're just looking at chest compressions or mouth to mouth resuscitation and there is no device involved at all other than your hands, your mouth, your -- then that does not fall under FDA's regulations as there is no device that is being studied. However, in the circumstance that you mentioned first with the I.V. fluid resuscitation, if you are randomizing to two different fluids types or concentrations and the protocol is delineating the randomization scheme, then an IND would be required.

>> Okay. Thank you very much. I think that's used up about all of our time. We thank you all again for participating. I would like to really thank our three speakers for doing a tremendous job of helping us all to better understand this opportunity we have to move research forward in emergency care in the provisions that are in place for us. I would encourage you all to follow up if you want to review this and go back to the archives and follow up to it and please be sure to complete your evaluation that will automatically be displayed here at the end. Thank you again and this will end our session. Goodbye.