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FOOD AND DRUG ADMINISTRATION
Public Hearing on Emergency Research and
Human Subject Protections
Challenges and Solutions

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University of Maryland College
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P R O C E E D I N G S

JEFFREY SHUREN: Good morning, everyone. Just ask everyone to take their seats. Can folks hear me in the back?

Okay. Good. Well, good morning. I'm Jeff Shuren, the Assistant Commissioner for Policy at the FDA, and I'd like to welcome you to today's hearing on emergency research conducted under FDA's regulation at 21 CFR 50.24. We're are very pleased that so many of you are here to participate in what we believe will be a helpful discussion of a complex and important subject.

I'm going to place emergency research in context and describe some of the general issues that are involved. Dr. Sara Goldkind, FDA's Senior Bioethicist, will then describe in more detail the history, regulatory framework, and FDA's ten-year experience with the current regulation, and she will also outline the steps we will take following today's meeting. Dr. Michael Carome, Associate Director for Regulatory Affairs in the Office for Human Research Protections, will make some specific points about the Department of Health and Humans Services' Secretarial waiver

of informed consent in certain emergency research. Following their remarks, we will turn to the real business of the day, and that's hearing from all of you about the ways in which the emergency research process has worked well, the challenges or difficulties you have encountered, and any suggestions you may have for improvements that can be made.

I think we should start by being clear about what we mean by emergency research. Emergency research for purposes of our discussion refers to planned studies involving patients who are in an imminently life-threatening situation that requires immediate intervention, who cannot give consent, and for whom there is either no proven or no satisfactory treatment. There must also be reason to think that the investigational product that would be administered holds the prospect of direct benefit for the patient. It is only in this very narrow situation that we have said that it may be appropriate to proceed without obtaining the informed consent of the patient. And yet, even in this extreme situation, the fact that so fundamental a right as the right to give consent will be suspended requires, in our

viewpoint, a number of additional protections for the patient. The purpose of all our efforts is doing what we believe is best for the individual patient as well as what may be best for other individuals who find themselves in similar circumstances in the future.

I'm a neurologist. I know there are many fellow health care providers present here today, and any one of us could find ourselves requiring emergency care one day. As practitioners, we know that many emergency conditions do not have proven or satisfactory treatments. We probably all have faced a situation of a very ill patient at death's door, who is unable to communicate, and no family members are present with whom we can consult. Something has to be done to help the patient, and time is of the essence. In these situations, it is possible that the patient's best alternative may be a product that is undergoing evaluation.

Although such use occurs every day in hospitals, clinics, and other settings in this country, often we don't know how well the treatment works. We are sometimes caring for patients in the dark because it is the best we can do.

Emergency research can help us determine whether

or not a treatment truly works, but it comes at a price. In this case, there is an inherent tension between two fundamental components of ethically sound research: the principle of beneficence and the principle of respect for persons. Emergency research promotes beneficence by using potentially promising interventions in the hope of helping the patient as well as by expanding our knowledge of what works and what does not work in treating future patients in these emergency settings and ultimately providing practitioners and patients with safe and effective products they can rely on.

On the other hand, the patients involved, because of their medical condition are unable to consent to their participation in research, and therefore it may be impossible to know what their wishes would be in these circumstances. In using the mechanisms provided in the regulation, we seek to honor the principle of respect for persons. All the parties involved--sponsors, investigators, IRBs, and FDA--have a shared responsibility for the protection of subjects, especially in the case of emergency research. The regulation imposes additional

responsibilities on all the parties involved, such as greater oversight by FDA, community consultation, public disclosure, and the establishment of a data monitoring committee.

Ten years ago, when we issued the final rule, we did our best to strike the right balance between the principles of beneficence and respect for persons by narrowly defining emergency research and providing a number of additional safeguards for subjects. We now have a body of experience with this rule, and we understand that there are concerns about how to implement and interpret some of its provisions and requirements.

We have issued a draft guidance to provide our current think on the rule to help better inform today's discussion. The guidance will also serve as an interim source of information as we consider what our next steps will be following the public discussion at this meeting and the comments we receive in our docket, both comments on the questions we asked in the notice of the meeting and comments on the draft guidance.

All of us here today are united by our common

concern for the safety and well-being of patients who find themselves in medical emergencies. We have called this meeting to hear your views about the conduct of emergency research, including what works in the rule, what may not work, and how might we make improvements. This is a listening session for FDA. We will not make any decisions today, and we do not have any preconceived ideas about how, from a policy perspective, we should proceed from here. This issues presented in emergency research, such as when are available treatments unsatisfactory, what constitutes adequate community consultation, even whether or not to conduct emergency research, are difficult and very sensitive for all involved. They invoke strong emotions, appropriately so, on all sides of this debate--in patients and their families, health care providers, researchers, IRBs, sponsors, and my fellow colleagues at FDA. We look forward to hearing your views on these issues to ensure that scientifically rigorous and ethically sound research can be conducted to develop effective and safe treatments to provide care for those whose lives are at greatest peril while demonstrating respect for persons.

And now I'd like to give you some housekeeping details. Today's meeting is being held in accordance with FDA's regulations in 21 CFR Part 15. Participants are asked not to interrupt other participants during the presentation, and questions will be presented or asked only by the FDA panel. We have seats set aside up front for the fourteen registered presenters so that they can more quickly go to the microphone. And I'd ask anyone who hasn't taken a seat there to please do so. The presenters will speak in alphabetical order. We have one exception just due to a scheduling conflict.

Each presenter will be given 15 minutes in which to speak, and I have a timer available. It's got a green, yellow, and red light. Just be on notice that the yellow light will go off when you have 2 minutes left, just to let you know how much time is left. And then the right light goes off and then--my apologies--there is a very annoying beeper at the end, should you run over. Hopefully, folks will not. And I just ask that you try to finish on time in fairness to others. Following each presentation, the FDA panel members may ask questions. In addition, we have

provided the presenters with the approximate time at which they will be speaking to try to make sure we stay on time.

At the end of this hearing, we will hold an open microphone session. I ask that those who wish to speak during this open session sign up at the table in the back of the room by noon. It's actually the table just outside the room here. After lunch, I will announce the number of individuals who will speak and the amount of time each has been allotted, and that will depend upon the number of folks who sign up.

I also want to remind everyone that the docket will remain open until November 27th, and you may submit comments on both the issues discussed today and on the agency's draft guidance until that date. I encourage you to do so, and we do take every comment into account. I hope also that everyone has registered at the table in the back of the room. It will just help us keep a record of the meeting. And I also want to make sure that you all get a copy of the materials that we have prepared, including a copy of the regulation and the presentations of the speakers. Those also can be found at the table in the back.

We will be breaking for lunch, and we have a list of restaurants. If you have not gotten it already, that also is at the back table. I know some folks may have to travel a little bit of a distance, and that's why we built in an hour and a half for lunch. Lastly, there is a café on the second floor of this building, if you wish to grab coffee.

Before moving forward, I just want to introduce our FDA panel for today, and actually the first person comes from the Department of Health and Human Services. It's Dr. Michael Carome. He is the Associate Director for Regulatory Affairs in the Office for Human Research Protections. To his left, is Catherine Lorraine, Director of Policy Development and Coordination Staff, the Office of Policy, Office of the Commissioner at FDA. Next to her is Dr. Sara Goldkind, Senior Bioethicist, Office of Critical Path Programs, Office of the Commissioner, FDA. Dr. Robert Temple, Associate Director for Medical Policy, Center for Drug Evaluation and Research, FDA. Dr. Joanne Less, Associate Director for Clinical Research and Government Affairs, Center for Devices and Radiological Health, FDA. Diane Maloney, Associate Director for Policy, Center for

Biologics Evaluation and Research, FDA. And Denise Zavagno, Associate Chief Counsel for Biologics, Office of Chief Counsel, Office of the Commissioner, FDA.

With that, let me turn to Drs. Goldkind and Carome.

SARA GOLDKIND: Before I begin, I'd like to take this opportunity to thank all of you for coming today and for offering your views both in an oral format, and we also encourage those of you who have not registered to speak, if you would like to, to please sign up do so. And if you would not like to speak, but would like to send in your comments, we would greatly appreciate those as well.

In this presentation, I'd like to build on some of the themes that Dr. Shuren has already introduced. I'm going to start with a brief section on the history and a focused look at 50.24, and then discuss in brief the experience that the FDA has had to date with this regulation. Dr. Carome will come and discuss particulars of the Secretarial waiver. And then we'll conclude with the issues that we hope to have addressed today and next steps following this meeting.

Many of you in this room have contributed to the historical development of this regulation, which actually dates back to the early 1990s, when at that time, it was recognized that there are unmet needs for treatment options in the emergency setting. It was also recognized that there was a need for explicit regulations to promote research to validate emergency treatment options. The FDA, at that time, sought in various manners input from the public, including representatives of patient advocacy organizations and the research community. FDA was advised that, without alternative informed consent procedures, emergency research could not be conducted, and therefore the safety and effectiveness of emergency treatment options could not be determined.

Some of the significant public input that we had in the early 1990s that led to the adoption of the regulation in 50.24 can be seen on this slide, and you all should have these PowerPoint presentations. They're at the front desk. It's a 1994 Congressional hearing which addressed problems encountered in securing informed consent of subjects, a 1994 coalition conference of acute

resuscitation and critical care researchers, and that conference resulted in a consensus document which offered recommendations. Those were submitted and reviewed by the FDA, and actually some of them made their way into the actual regulation itself. In 1995, FDA and NIH cosponsored a public forum on emergency research, and the office at that time, at NIH, which participated with FDA in cosponsoring that public forum, was the predecessor office to OHRP now.

Many participants expressed at that time concern that the current regulations value individual autonomy and the right to informed consent at the expense of the principles of beneficence and justice. And we're going to talk a little bit more about the regulation in reference to these ethical principles in a minute. The majority of participants supported new regulations to clearly permit the waiver of informed consent for acute care research if certain defined conditions and safeguards are met. All of this public input and careful thought led to the regulations in 1996. They're called 21 CFR 50.24. And also in 1996, HHS announced its Secretarial emergency research consent waiver.

In addition, FDA has issued two different draft guidances: one in the year 2000, and recently we updated the draft guidance, recognizing that it's an interim source of information. We felt that we had valuable contributions to share with you all based on our experience to date, and we wanted to also provide a context for today's discussions, but we recognize that there will be a lot that we may learn from today's meeting and that there may eventually be changes and updates in those particular documents as well.

So, now I'd like to talk a little bit about the ethical principles of respect for persons and beneficence. And I've taken these two quotes directly from the Belmont Report, which many of you know was issued by the National Commission in the 1970s. In that document, it defines beneficence as "persons are treated in an ethical, not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being." The problem posed by the imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved and when the benefits should be forgone because of the risks.

Respect for persons, as said by the Belmont Report, incorporates at least two ethical convictions: "Individuals should be treated as autonomous agents," and "persons with diminished autonomy are entitled to protections."

What I'd like to submit is that there's a certain tension that we have tried to balance between beneficence and respect for persons as found in 50.24. One of the questions we're asking today is, should these principles be balanced any differently than they are currently in the regulations, and, if so, how?

So, now turning to a focused look at 50.24 in light of these two principles, I'm not going to go through the regulation in detail. You've all been supplied with a copy of it. But I'd like to hit on a few highlights.

One highlight is that, given that informed consent is unobtainable, 50.24 requires additional protections to further safeguard patients. IRBs, clinical investigators, sponsors, and FDA have increased responsibility for implementation of these additional protections. In other words, all oversight bodies have ratcheted-up

responsibilities given the fact that informed consent is waived.

So, what I've done, in the next few slides, is listed a few, in a bulleted fashion, a few of the stipulations from 50.24, which I think supports beneficence or respect for persons.

First of all, looking at beneficence, the fact that the subjects are in a life-threatening situation, that available treatments are unproven or unsatisfactory, and that evidence supports prospective direct benefit to the subjects--all contribute to the respect for the principle of beneficence. Additionally, risks associated with the intervention are reasonable in relation to risks and benefits associated with the subject's current medical condition, standard therapy if any exists, and the proposed intervention or activity itself. As well, as part of the honoring of the principle of beneficence, this particular regulation requires a mandatory establishment of an independent data monitoring committee to review, in a predefined manner, safety concerns throughout the trial.

Now, this is the only regulation that requires a

data monitoring committee. Many times, sponsors and the FDA elect to use a data monitoring committee for a particular study, but according to this regulation, it's mandatory.

Now looking at respect for persons, I would submit that the investigator has committed to attempting to contact the legally authorized representative for each subject and, if not feasible to do so, the subject's family member. Providing them the opportunity to object is one manner in which respect for persons is honored. Additionally, the IRB has to review and approve procedures for obtaining and documenting informed consent from either the subject, if he or she becomes able to provide it, or the legally authorized representative. The IRB has to review and approve procedures for providing an opportunity for a family member to object to a subject's participation and also procedures for informing subjects, the legally authorized representative, or family member of a subject's inclusion in the trial and the right to discontinue that participation.

Additionally, respect for persons is honored by consultation with representatives of the communities in which the clinical investigation will be conducted and from

which the subjects will be drawn. The fact that there must be public disclosure to the communities prior to the intervention and the fact that there must be public disclosure of sufficient information following completion of the trial to apprise the community and researchers of the study.

So now turning to our experience. Since 1996, in the past 10 years, FDA has received a total of 56 submissions to use the rule. Those submissions have gone to CDRH, CDER, and CBER. Of those 56 total submissions, only 21 of the studies have actually either been conducted, are currently being conducted, or are about to enroll. There are a few trials that have not enrolled yet. Of those 21 trials, the majority of them are actually still being conducted.

Now, some of the reasons for the studies not being conducted--I tried to highlight these in red, but I'm not sure how well it's transmitting--is the fact that the studies don't meet the requirements of 50.24 or the fact that the studies don't meet the requirements of either the IND or IDE regulations, under which they have to be

submitted to the FDA as well. When these studies are submitted, they're submitted with a special letter that has to accompany them, making note of the fact that the proposal includes subjects who would not be able to give informed consent.

The FDA reviews these submissions very carefully under 50.24 regulatory requirements, but, in addition, all of these studies have to be submitted either under the IND, Investigational New Drug, application regulations or under the IDE regulations for devices. And the studies have to be considered separately under those as we would do for any other study.

The majority of the reasons why they don't go forward relates to the fact that they don't meet one or the other of those regulatory requirements. However, other reasons that they may not go forward is they're not approved by the IRBs of record, who review them after they've been given the go-ahead by the FDA, or because of sponsor withdrawal for whatever reason the sponsor decides not to go forward with the trial.

I also, going back to this slide, would like to

mention that, since April of 2006, there have been approximately 2700 subjects enrolled in these 21 trials. That's an approximate figure because, as I said, the majority of these trials are ongoing, so some subjects may decide to withdraw, or their family members or their legally authorized representatives, and additional subjects may actually be enrolled since April of '06. But that's an approximate figure, so you'll understand the enrollment to date.

So, what have we found at the FDA in terms of the usefulness of this regulation? We have found that the studies have allowed the conduct of research in a number of critical areas that could not otherwise have been done, such as improving brain recovery after cardiac arrest or head injury, treatment of acute liver failure, treatment of traumatic hemorrhagic shock, treatment of hypovolemic shock following blunt trauma, and public access automated defibrillation post-cardiac arrest, the defibrillators that you see in the hospitals and schools and public buildings. The public access of those defibrillators came as a result of these trials.

It's also this research has contributed to peer-reviewed literature on informed consent issues in emergency research, the ethical aspects of that, as well as on medical knowledge about emergency interventions. And given the fact that very few trials have been completed to date in this arena, we've had two approvals so far: the Concentric Retrieval System for retrieval of thrombus from the neurovasculature, a device that pulls a clot out of the brain, which I am told appeared on the Emergency Room TV show; and the Automated External Defibrillators for public access.

So, without further ado, I'm going to turn the podium over to Dr. Carome.

MICHAEL CAROME: Good morning. I just want to make a few comments about the Secretarial waiver of the informed consent provisions for certain emergency research.

By way of background, there's a provision in the Department of Health and Human Services' regulations at 45 CFR 46.101(i), which permits the Secretary of Health and Human Services to waive the applicability of some or all of the provisions of the human subject protection regulations. And

so, on October 2nd, 1996, simultaneous with the FDA issuing its final rule at 50.24, HHS published a Federal Register notice announcing a waiver under the provisions of 46.101(i) of the following requirements for certain emergency research, and those are the requirements for obtaining informed consent and the requirements for documenting informed consent for certain emergency research. And this waiver applies to research conducted or supported by HHS, for example, NIH-supported research.

Just in terms of a couple of key differences or features to be aware of in the Secretarial waiver in comparison to the FDA rule, the Secretarial waiver for emergency research is not applicable to HHS-supported research involving pregnant women, fetuses, or prisoners. Secondly, if the research does apply, that is, it involves certain emergency research and doesn't involve those three populations of subjects and the research is conducted or supported by the FDA, so there's dual jurisdiction of HHS and FDA, then the provisions of 21 CFR 50.24 must be satisfied. So that the waiver essentially defers to the FDA regulation.

If the research is not FDA-regulated, then the IRB must find and document and report to OHRP that specified conditions, essentially identical to the provisions of 50.24, have been met.

In terms of next steps for OHRP, we plan to seek public comment on the current Secretarial waiver of informed consent for certain emergency research, and when considering whether any of those provisions of that waiver should be changed, we will work closely with the FDA to ensure that FDA's rule and the provisions of the Secretarial waiver remain consistent. Thank you.

SARA GOLDKIND: So, today, what are the issues that need to be addressed? We hope to learn more about the challenges of conducting clinical emergency research and possible solutions to those challenges. And in writing the Federal Register notice, the meeting announcement, for this meeting, we took into consideration a vast array of previously recorded thoughts and materials. We've scoured the peer-reviewed literature for information on emergency research as well as comments that the agency had received, and we came up with the following big-ticket items. There

are many in the Federal Register notice. There are a total of 21 questions, many of them have subparts to them.

The adequacy of human subject protections under 50.24 and, in particular, the interpretation of terminology such as "unsatisfactory or unproven," "practicably," and "prospect of direct benefit."

We would like to further clarify responsibilities of IRBs, clinical investigators, and sponsors.

We'd like to look carefully at community consultation: the costs, benefits, feasibility, and effectiveness of it; whether minimum requirements are necessary or should be a standard; use of information obtained during that process, how will it be used and by whom; and how will the end results of the community consultation process be documented and will there be a mechanism for public disclosure of those community consultation activities?

Currently, the regulation 50.24 requires that public disclosure information, which is the one-way communication between the sponsor and the community, be documented and submitted to the federal FDA docket, but that

same requirement does not currently exist for community consultation, which is a two-way communication process between the sponsor and the communities, as I've described.

We want to look further at public disclosure and whether minimum requirements should be a standard there and, if so, what should they be; if there should be anything further in terms of submission of public disclosure information beyond publication in the FDA docket; and how best to publicly disclose research results once trials are completed.

We want to find out further thoughts on opt-out mechanisms. Currently, this regulation can be understood as an opt-in, that everyone who meets the specifications in that regulation can be a part of these trials. We want to find out whether there should be opt-out mechanisms, whether they're necessary and, if they are necessary, are they actually feasible?

And then we want to discuss whether there are other types of public discussion that should occur prior to initiating the study. Is that type of public discussion needed? If so, in what circumstances should it occur? And

if so, what would be the best venue for these discussions?

As Dr. Shuren already alluded to, we're going to amass the information that we get either via written comment or presentations here today. We're going to carefully review all the comments submitted to the FDA docket in relation to this meeting. We're also going to review all the comments submitted to the FDA docket in relation to the draft guidance, and carefully evaluate all the options that respond to the received feedback.

So, once again, thank you very much, and we welcome you submitting your comments, either in written form or orally today.

JEFFREY SHUREN: Thank you. Why don't we go ahead and start with the first presenter, Dr. Michelle Biros from the Society for Academic Emergency Medicine and the Coalition for Acute Resuscitation Researchers.

MICHELLE BIROS: Good morning. The Society for Academic Emergency Medicine is grateful for this opportunity to provide comments from its membership to the FDA related to the exception from informed consent in emergency research circumstances. The Coalition of Acute Resuscitation

Researchers joins SAEM in this presentation. We also include comments from the American Academy of Emergency Medicine.

In 1994, SAEM took the lead in discussions related to issues of consent in emergency research. The coalition was developed at the request of SAEM to broaden these discussions and included thought leaders from throughout the research community. The coalition developed a consensus document that was subsequently endorsed by over 25 professional organizations concerned with emergency research, and presented concepts that were eventually incorporated into the FDA's final rule.

Since the codification of the final rule into federal regulations in 1996, SAEM has continued to discuss, educate its members, and monitor the use of the final rule within the emergency research community. In May 2006, SAEM's official journal, *Academic Emergency Medicine*, sponsored a consensus conference entitled "The Ethical Conduct of Resuscitation Research: Exception from Informed Consent." The proceedings of the conference were published in the November 2005 issue of *AEM* and widely disseminated.

This issue of the journal also includes original research on the application, interpretation, and attitudes related to the final rule.

With this background in mind, we feel well qualified to offer these comments related to the 2006 FDA guidance document to address specific issues raised by the FDA and to offer additional questions of our own. In so doing, we must recognize that the 2006 guidance document is fashioned around the rule as it currently exists. We strongly believe that a better approach would be to revisit the rule itself and use existing experience and data to determine whether and where it meets its goals and where requirements have missed the mark.

The FDA has asked a number of questions today. We're briefly mentioning a few areas so that we can provide focused thoughts related to the issue of exception from informed consent. The FDA has asked if there are challenges that have not been explicitly addressed in the regulations and if these challenges should be addressed now. We believe that there are many challenges that have not yet been addressed by the regulations. Some relate to specific

patient populations that are not considered in the final rule, such as children. Yet, in the decade since the final rule was implemented, our society and the emergent illnesses and injuries that we face have changed.

Children are now as likely as adults to be victims of life-threatening or high-morbidity events, such as gunshot wounds, terrorist attacks, illicit drug overdoses, or emerging infectious diseases. Children also suffer from life-threatening illnesses or injuries that are rarely seen in adults and which have been poorly studied. Restricting pediatric resuscitation research to only those circumstances for which consent can be obtained would limit the research questions we can ask, narrow the methodologies we could apply, and bias the results that we obtain.

It is also erroneous to assume that all children who present with emergencies will be accompanied by parents or guardians who can provide informed consent. Many of these children are brought to hospitals unaccompanied, and many have parents or guardians who are far too distraught to be approached for informed consent within a narrow therapeutic time window. To deny children the possibility

of direct benefit through participation in resuscitation research contradicts the FDA's mandate to include children in research and frankly is unethical. We believe that a better guidance on the application of the exception or a reconsideration of the rule's requirements in order to address issues in special populations such as children is paramount. Resuscitation research also includes studies of varying complexity across a wide spectrum of clinical pathologies. As medical care advances and new knowledge is developed, the risks and benefits of particular interventions should change. Previously highly fatal events may become critical high-morbidity events instead. It is an ethical and moral medical imperative not only to save lives but to improve the quality of life.

While the final rule allows for research in high-morbidity events, these may be very difficult to predict and--or in fact even to define as the clinic spectrum changes. One set of regulations is not appropriate for all studies, and we believe that the concept of incremental risk assessment should be considered.

Other challenges relate to changes in the research

environment itself, and the final rule currently offers no room for growth, for unanticipated developments, or for change based on experience and data regarding its use. For example, the Institute of Medicine's recent report on the future of emergency care describes a lack of clinical effectiveness trials for the treatment of critically ill or injured patients in the out-of-hospital setting.

We have a growing cadre of EMS research expertise, and some studies using the final rule have been completed in the out-of-hospital setting. Yet, we also have data that suggest fulfilling requirements of the final rule in the out-of-hospital setting is inconsistent, even within the same EMS system. We must ask the EMS research community itself what unique challenges they have encountered and determine if the regulations address these unique aspects of out-of-hospital research. Should the same set of regulations apply to all clinical environments that have unique challenges and unique patient populations served?

The translational emphasis of the NIH has led to the development of at least three emergency-based research networks, who will present testimony later. All aim to test

new treatments for critical illness or injury. Many of the studies undertaken by these networks will require using the exception from informed consent. Challenges are always present when you try to successfully and consistently implement a study protocol in many sites. And what we need to do is to determine the unique challenges that will arise when the exception from informed consent is applied across a network. For instance, there are variable levels of comfort and expertise among IRBs regarding the use of the exception from informed consent. The final rule rests increased responsibility and authority into IRBs, but the details of this regulation are very complex, and to date, IRBs have been given limited guidance and very little feedback.

Is it reasonable to expect that all IRBs will achieve a working knowledge of this complex and infrequently used rule? How can we ensure a consistent and fair protocol review at all sites? Some IRBs either refuse or are very reluctant to allow research using the exception, which results in a demographic bias in study enrollment. Therefore, we must consider whether a central IRB be established for network studies. What are the practical and

ethical implications of a central IRB and how should it be formed? These are very tough questions with very significant clinical and ethical implications.

These are just a few of the many challenges that were never anticipated when we wrote the final rule, and now is the time to address them. Failure to do so is scientifically worrisome and ethically dangerous.

The FDA has also asked a series of questions about community consultation as a patient safeguard. While the concept of community consultation is attractive and in theory allows community values to be factored into the research process, the reality is that community consultation has been consistently problematic. We have essentially no evidence to show that it is effective in its goals and, in fact, much evidence to suggest otherwise.

In the decade since the final rule was established, less than a dozen studies have examined the methodologies of community consultation, and these have been poorly undertaken and have been published very sporadically.

These studies have documented the ambiguities inherent in community consultation and also the lack of appropriate

evaluation methods to assess the adequacy of the process. The goal of community consultation is to elicit the opinion of the community related to a research protocol and to use the information obtained to deliberate on any concerns before the study is implemented. In order to provide useful discussion, the community should understand the protocols under consideration. But data from the public access defibrillation trial suggests that even members of focus groups with multiple educational sessions do not generally understand the goals of the study or the actual protocols that would be undertaken. The final rule asks for community consultation, but we have not required a measure of its effectiveness.

How, then, do we make sure that the community understands? To our knowledge, there's no formal reporting required of how community consultation has altered protocols using exception, and we have very little information on how IRBs use the information provided in consultation. If we do not measure the effectiveness of our community consultation efforts, how do we know if we have indeed protected patients at all?

We also suspect that the methods used to achieve community consultation have not resulted in broad representation of the community of potential subjects or the community in which the research will be conducted. Studies have documented that this process results in very few people attending public meetings, and those who do attend such meetings are likely to be non-representative of the at-risk population. For example, we conducted at my institution a study of a drug to sedate acutely agitated, delirious, cocaine-intoxicated patients. Despite great effort, we could not recruit a single cocaine addict to participate in community consultation. Who then in a community is providing us the feedback we need? And does it reflect the true concerns of the targeted study population? How do we know that we have heard their concerns since we are not required to measure this?

If community understanding is lacking and involvement is non-representative, the goals of community consultation are not met and it becomes a cumbersome and futile exercise. Given a decade of experience with the rule, we must revisit the actual intent of community

consultation and determine if its purpose is still meaningful. We do not believe it will be easy or possible even to determine if community consultation provides adequate patient safeguards against research risks since there are no specific measures of its effectiveness and very few ways in which we can quantify it. Therefore, instead of asking if community consultation provides adequate patient safeguards, the better question probably is, how can we better protect patients?

Public notification and disclosure are other safeguards built into the final rule. Disclosure of full research protocol or of specific scientific information to the public may cause concerns similar to what I have already noted. However, the intent of public notification is different. It is disclosure, and not a discussion. If we include protocol specifics or specific scientific information to the public, how can we be sure that they understand what they hear? Does the public really need to know specific details? Even more basic, how can we be sure that this information actually reaches the public as the process was intended? As an example, we interviewed

patients in emergency department waiting rooms in three large cities after a very aggressive and widespread public notification campaign had been conducted regarding a study using exception from informed consent. Less than 5 percent of individuals surveyed at any of the sites knew that the protocol existed.

The balance between meaningful individual patient protection and the potential societal benefit of conducting research without consent is essential and part of our key values as emergency researchers and practitioners. Whether this is achieved by the final rule in its present state in a patient-protective manner remains unknown.

We appreciate the FDA's willingness to listen to our comments and hope this information will provide useful to the FDA and assist in reducing some of the existing barriers to resuscitation research. However, we appeal to the FDA to seriously reassess the final rule itself in light of our concerns that it is not effectively and meaningfully providing the safeguards for vulnerable patients as it was intended to do. Just as it is our medical responsibility to constantly expand our knowledge and treatment strategies and

to learn from our research, we also believe it is our responsibility to reassess the ethics and the rules by which research is conducted.

In conclusion, SAEM, its concurring partners in the Coalition of Resuscitation Researchers request that the FDA convene a meeting of stakeholders, similar to what occurred 10 years ago, and revisit the requirements of the rule for conducting research without consent in special emergency circumstances. The goal of this process should be to inquire broadly into the experiences of implementing the rule to date and to factor in that experience into a rule of the future. Thought leaders must be brought together to discuss how to better meet the needs of our vulnerable patients within an evolving research environment. Thank you.

JEFFREY SHUREN: Thank you. Let me ask, in the beginning you had talked about that we should maybe consider an incremental risk assessment and that there may be flexibility on where you sort of draw the line on when emergency research may be appropriate. Could you elaborate a little bit more on it and maybe tell us if there are

particular factors that we should take into consideration? I think one of the things you put on the table is there's a need for greater guidance for others, you had pointed out IRBs in particular, as to when it may be appropriate to conduct emergency research. And as we consider something that may be incremental, that might actually be a little bit more difficult to do. So, what guidance could you give us, were we to actually consider an incremental risk assessment?

MICHELLE BIROS: Incremental risk was one of the concepts presented in the consensus document that we developed about 10 years ago. When you look at the regulations, when certain IRBs have looked at the regulations, they are, they assume that the assessment should be based on the risk of the research relative to the patient's critical condition. In a sense that means that the sicker the patients are, the more risky you can get. And I think there has to be a better understanding of the gradation of various types of pathologies that we see, and assess that particular pathology in terms of the risk/benefit ratio of that, the person that we see in front of us, and not in general categories.

There have been a number of people who have discussed modeling systems related to incremental risks, and so there's a number of discussions that do actually occur in the literature.

SARA GOLDKIND: You mentioned that the regulation should provide room for special populations, particularly children, and also you mentioned that, the need perhaps to institute a centralized IRB for multi-site trials, but I'd like to ask you for more clarification in both of those regards because the current regulation does allow for pediatric studies and could allow for a centralized IRB. But what I'd really like to get back from you, because I know you're in the field trying to do this research, is how you go from the regulation to practice, to implementing this research and why is that--and how could the communication be more effective so that it is known that children can be a part of emergency research? And centralized IRBs are certainly acceptable.

MICHELLE BIROS: That is a very interesting question. I believe that most IRBs have not considered this regulation at all for pediatric cases. So, the key question

of communication and guidance of IRBs is really important. Related to--what--I think when you take look at research in general, resuscitation research is a small part of that pie, and those studies which would require an exception from informed consent is even a smaller piece. There are thousands of people on IRBs who have minimal understanding of existing regulations that they work with on a daily basis and absolutely no experience or no understanding at all of the final rule that we are talking about today. So, there has been a gap in the knowledge that is provided. It's been our, SAEM's stance on several occasions to talk to the researchers and say, "You need to educate the IRBs about these regulations." But whether or not that is realistic is another question.

When it comes to considering a central IRB, perhaps a better way to evaluate or call this would be a "central advisory committee" that could provide specific guidance to IRBs who are currently investigating or assessing regulations related to the final rule in terms of a protocol right in front of them. And so, I think there needs to some sort of a central body that will provide

experience and understanding to IRBs as cases arise, on a case-by-case basis.

SARA GOLDKIND: Thank you.

JEFFREY SHUREN: Other questions? Bob?

ROBERT TEMPLE: Yeah. You spoke at some length about the difficulties of community consultation, what it means. You stressed that we don't really know much about its success. From the context of your comments, however, I don't believe you were asking us to insist that people document the success. So, I would like to know a little more about what your proposal is. Do you think that it should not be required in some cases or that the requirement should be modified or that somebody should conduct independent studies to find out the best way to do it? I realize you're--we all, we recognize that it's the most difficult part of the rule in some ways.

MICHELLE BIROS: Well, I think that when investigators, sponsors, and IRBs approach a study in which exception is going to be applied for, the community consultation piece is the hardest part, as you've indicated. I don't think I'm suggesting that we do away with patient

safeguards. My question and my concern would be to actually document and talk to researchers who have engaged in studies that have used the exception from informed consent, to find out what aspects of community consultation really worked and what didn't. If you read the literature, they very briefly will describe how community consultation was performed, such as "We convened meetings of patients who had previously experienced the specific pathologies." But there isn't much of documentation record that we are aware of indicating how many people came to those meetings, what the specific questions were, and whether or not those questions had any impact at all on IRB deliberations. So, I'm not convinced, and I don't think many researchers are convinced, that community consultation is practically providing patient safeguards.

It currently is considered a step to the end, and that's not what we want it to be. So, my suggestion would be that we convene a meeting of researchers who have gone through this process and discuss and brainstorm for possible other patient safeguards that might meet the same end, but that we could quantify and track to see whether or not data

supports the use of these particular techniques.

JEFFREY SHUREN: Diane?

DIANE MALONEY: I want to say--just to follow up on that question in terms of community consultation and sort of the, you know, again, this is all about patient protection, and what values do you see might added from having like a public meeting and advisory committee meeting discussing these kinds of studies?

MICHELLE BIROS: In terms of a replacement for community consultation?

DIANE MALONEY: Well, it could be in addition to. Again, you know, some of this is you haven't had a lot of participation. I think you're pointing out not a lot of people come. If it were discussed in, you know, say, an advisory committee meeting, I think more people would come. It would be maybe a different focus, but what would you see would be--if it were in addition to--the advantages of that or disadvantages?

MICHELLE BIROS: Well, I think we have to very carefully consider who comprises the advisory board. So, for instance, I work at a hospital that services an inner-

city population. It would not be useful to me to be told by an advisory board to do a, you know, random phone campaign, because my patients don't have phones; or to ask them to come to public meetings when they have no transportation. So, I think there needs to be a further assessment of what has happened so far; what seems to work, which really doesn't work; and, again, not view a community consultation as another step to the end product, but rather as a patient safeguard, and determine if it truly is guarding patients from risks of research. I would like to know if IRBs have actually spent time considering those comments and changing a protocol or if we have any data whatsoever that it has actually protected patients.

Rather than make it another step, I think we need to make a safeguard. I'm not convinced that community consultation is the way we need to go. I can't give you an answer. I think we need to sit down with thought leaders that have broad experience and determine what has, they have attempted and what hasn't, and also with biomedical ethicists as well as medical practitioners and researchers to see what they believe might constitute a very good

patient protection.

DIANE MALONEY: Can I also, I just have a follow-up question. In terms of, again, in human subject protection, a lot of the things we focus on is the community attitudes and input from the local community, but we also, in terms of looking at this rule, people have pointed out that in terms of the information that has been provided in community consultations, it has varied in terms of the level. Do you, could you just comment on your thoughts on whether you think there's a minimal amount of information that ought to be provided in these consultations and discussions with communities?

MICHELE BIROS: Again, I think you have to grade this on a case-by-case basis and also the patient population you're targeting. If, for instance, the patient population that is at risk of a particular pathology tends to be people who have limited access to health care, for instance, it's going to--you're going to have provide a different level of information and provide different discussion points than you would for a highly sophisticated audience who have primary physicians. I don't think you can make a blanket case for

anything. And that's one of the issues that IRBs have to grapple with when they consider these particular protocols.

JEFFREY SHUREN: Thank you very much. Next I'll call Dr. Charles Cairns and Dr. Edward Sloan of the American College of Emergency Physicians.

CHARLES CAIRNS: Thank you. I am Dr. Charles Cairns from Duke University, and I represent the American College of Emergency Physicians. My colleague Ed Sloan sends his regrets. He was unable to attend today's meeting because of horrible difficulties. In addition, we'd like to recognize and appreciate the comments of our colleagues from the Society for Academic Emergency Medicine, and you'll find our remarks are consistent with their comments.

Today the American College of Emergency Physicians greatly appreciates the opportunity to revisit the exception from informed consent for emergency research and the opportunity to comment on the draft guidelines.

The American College of Emergency Physicians believes that the draft guidance has been responsive to researchers' concerns and has helped clarify the requirements of federal legislation. Emergency research

advances the field of emergency medicine. It improves clinical acute care. Emergency research should be supported in whatever means are possible, including the use of the consent exception and the guidelines that govern its use. The recently released Institute of Medicine report on the future of emergency care describes the scarcity of clinical effectiveness trials for the treatment of critically ill or injured patients. Thus, the continued conduct of research in this setting, particularly the pre-hospital setting, is critical.

We also agree with our colleagues from SAEM on the need for additional research in areas such as resuscitation, where new strategies, such as therapeutic hypothermia, have great promise to improve patient outcomes. Yet, research in this area cannot proceed without appropriate mechanisms for that research, including consent.

Now, regarding the work of federal agencies, including the FDA, the NIH, as well as IRBs to date, the American College of Emergency Physicians believes that these agencies that have been responsible for research guidance and support have done an excellent job in crafting the

regulations and working with investigators to implement them in the support of the quality of emergency research.

In addition, the American College of Emergency Physicians looks forward to working with all concerned federal agencies, local IRBs and advocacy groups, all emergency health care societies and providers, as well as individual citizens, as we strive to improve patient outcomes through the conduct of ethical and effective emergency research that utilizes the exception to informed consent. In addition, any revisions to the current guidelines should serve to expand the ability to perform the highest quality emergency research and to enhance patient protections through fairness, openness, and the use of all media that provide explicit detail regarding the research. The burden should not be placed upon researchers in a way that is disproportionate to the inherent risks and needs to advance emergency care through the conduct of quality emergency research that uses the exception.

Now, in response to specific FDA questions, for example on community consultation, ACEP believes that the use of community consultation is relatively new in research

and merits further study. While the overall processes have been well received, many unresolved issues remain, such as which community to consult? Who counts as a community representative or a member to be consulted with? And what is the purpose of this consultation? An important step is to conduct research on community consultation in order to identify best practices before we can provide further guidance on this issue.

In addition, the American College of Emergency Physicians suggests that if the goals of community consultation and public disclosure could be more clearly defined, then these goals would also guide investigators and sponsors in enhancing the processes of conducting clinical trials while providing quality emergency care to those patients.

Regarding the opt-out provision, the American College of Emergency Physicians suggests that the current opt-out mechanisms may be necessary, but not necessarily sufficient to identify patients deferring participation in the research inclusion. Although patients in extremis cannot be assumed to be competent to provide informed

consent, they should be assumed to be competent to refuse participation in research that utilizes the exception, the so-called consent to continue provision. As such, the American College of Emergency Physicians suggests that patients should be briefly asked if they wish to participate in the research, and if they decline to participate, then their wishes should be honored.

With regards to the question on information obtained during community consult processes, the American College of Emergency Physicians believes that community consultation can not only provide on the study, but could actually help the local IRBs further identify risks and then to protect patients from those risks of the research.

ACEP, or the American College of Emergency Physicians, suggests that the use of the exemption must be explicitly stated to all who might be at risk or those who might benefit from the research, including the hospital, its staff, the IRB, the population of potential patients who might become involved in the research, and the governmental agencies that might oversee the research. This includes full notification of the results of all IRB deliberations,

including those who decline to participate, the results of community consultations, and public disclosure and results of the clinical trial itself.

Furthermore, we suggest there should be a record of all suggestions generated by community consultation and how the IRB and investigator handled them. This documentation could or should be the responsibility of the sponsor and be publicly available, potentially on the FDA Web site or through a site such as clinicaltrials.gov.

Regarding the questions on protocol availability, the American College of Emergency Physicians believes that, while full study protocols do not necessarily need to be formally presented at these communities or even to the general public, these study protocols should be available upon request.

On the question on the disclosure of study results, the American College of Emergency Physicians believes that results of clinical investigation should be disclosed when the study has been peer-reviewed and ready for publication. The results of all studies that utilize the exception of informed consent should be published in the

medical literature, even if the results of the clinical trial do not demonstrate benefit with the tested therapy or procedure. ACEP encourages journal editors to support publication of negative trials that utilize the exemption in order to assist with the process of utilizing this route of research.

So, in summary, the American College of Emergency Physicians fully supports the processes necessary to conduct high-quality emergency research, including this review of the exception to informed consent process. It is through continued dialogue on important matters such as this that clinical science will improve emergency care and optimize outcomes for acute care patients. Thank you again for this opportunity.

JEFFREY SHUREN: Thank you. I have two questions. You had first talked about community consultation, and one of the issues here is to sort of clarify the goals and purpose of community consultation. Let me sort of phrase it a different way because, you know, we've heard comments from before, too, about what is the value of community consultation, what does it serve?

Let's put it aside. There are additional safeguards put into the regulation. Let's say those were to remain the same for argument's sake. What, from your perspective then, is missing by way of additional safeguards and how would that be addressed?

CHARLES CAIRNS: I think my comments are going to reflect those of Dr. Biros. Clearly, one of the challenges of doing the community consultation has been the fact that most of these sessions have not been well attended. They don't appear to represent the community that's being researched, and so it's unclear if they're actually effecting a communication of the purposes of the research, the benefits and risks to those who might participate in it.

So, there may be more effective strategies to enhance patient protections of not only those patients but to reflect the community interests. In doing individual meetings, at least in our experience, and the experience of many researchers for the American College of Emergency Physicians has been that they are currently poorly attended, they don't represent the community, and those goals have not been achieved--necessarily achieved.

JEFFREY SHUREN: So then, just to clarify, what I'm hearing then is it's very important to engage a community where such research would be conducted, but what is currently laid out in the regulations or explained through guidance may not be the best mechanism by which to achieve that. Is that a fair characterization?

CHARLES CAIRNS: Fair characterization. And we would go further to say that there's an opportunity to do further research, gain from the experience of those who have conducted such research, and develop best practices, which could then be shared to best achieve the goals as stated in terms of community consultation.

JEFFREY SHUREN: And my second question was on opt-out. You had talked about how every subject should be asked if they wish to participate. Certainly, during the study itself, we're talking about individuals who cannot give informed consent. Can you just elaborate on what you had in mind?

CHARLES CAIRNS: Yes. In fact, I'm going to refer to my colleague Ed Sloan's literature that he published in *Academic Emergency Medicine* in December of 1999, where he

outlined the process for the consent procedure in the diaspirin cross-linked hemoglobin trial. As part of that procedure, every patient who was at all conscious or responsive was asked whether or not they wanted to continue in the study. He deemed this process the consent to continue to participation in the trial. So, these are patients, because of their clinical condition, in this case hypoperfusion and potentially the inability to fully process information, at least to have an opportunity, from whatever baseline status they were, to say whether or not they wanted to continue to be in a research study. It should be noted that the vast majority of patients who were approached in that trial with this question agreed to continue.

So that's--I think that Dr. Sloan's additional comments on that would be that we realize that going through a complete consent process, including demonstrating full understanding and recognition of the challenges, benefits, and details of the trial, may not be possible in someone in hemorrhagic shock and who's not perfusing their brain adequately to supply that. They should at least just be given an opportunity to understand that something other than

standard clinical care is occurring.

JEFFREY SHUREN: Questions from others? Bob?

ROBERT TEMPLE: On that last point, there already is a requirement that when a patient does become capable of giving consent, that they be asked about their willingness to continue. Are you referring to that or to moving that point earlier in time, when a person shows at least a glimmer of awareness, or are you referring to bits of consciousness that might be present even at the time of the initial, of the initiation of the study?

CHARLES CAIRNS: I think it's a very challenging endeavor, how one would actually operationalize this, and Dr. Sloan noted that, in the case of hemorrhagic shock, it may be special, because you can have some perfusion of the brain, and while it may not be your full faculties, you may be able to at least understand and speak. So, in his case, whenever there was evidence of consciousness, that they would then, all patients would be asked about this approach. He deemed this the consent to continue, and while it's not necessarily part of the language of the provision, clearly I think it's a stated goal provision, that all subjects should

be approached. They just decided to extend it and try to ask everyone.

ROBERT TEMPLE: So I--it sounds to me like you're really raising the question of who is it that actually can't give consent, how obtunded do you have to be before--I mean it's partly who's allowed to be under this provision?

Okay. That's helpful. And I was also still curious about the opt-out. That's been an area of considerable controversy, and there's doubt about whether you can administer that. Apart from the thing we've just been discussing, did you have suggestions more broadly on opt-out, like, are you advocating that everybody who enters a hospital be asked about any studies ongoing? Or what were you proposing there that's different from what's being done now?

CHARLES CAIRNS: I think the key, the challenge with be opt-out--and actually my comments weren't directed specifically to the opt-out other than to say that the opt-out mechanisms that are currently in place may be necessary, that the challenge of opt-out--and having been a researcher who's done this work--is that most of the opt-out requests,

at least in our case, came from people who would not possibly be participating in the trials, people from other states who were nowhere near our locality. And so, the application of trying to opt out those people from a study in our local region are just tremendous.

ROBERT TEMPLE: And then the last question, I just needed, we just needed to be very sure on this: You, like Dr. Biros, had been somewhat critical of the whole awareness of what actually comes from community consultation. We need to understand whether people are proposing that we put more requirements in place for making sure community consultation works or are you so skeptical about it that you don't think we should do anything of that kind? It doesn't strike me in general that what you'd like to see is more clear requirements, but we need to understand which is being proposed here.

CHARLES CAIRNS: If I was interpreted as being critical, then I didn't clarify my position. We think that overall the processes have been well received in terms of trying to get community consultation. However, we think there can be improvements to that process and that part of

that process of improving it would be to convene some sort of experience, whether that be in a panel form, whether that be from the literature. Hopefully, that being from a scientifically based study of the community consultation process. And once those best practices are identified, studied, and reinforced, to make sure that those, the principles that are put into the draft guidance. So, an evidence-based approach to the draft guidance on community consultation.

JEFFREY SHUREN: Joanne?

JOANNE LESS: I just wanted to follow up on your comments on community consultation. You had said in your notes that you were proposing sort of that more information be presented and discussed and additional identification of risks and how they might be mitigated. Given some of the earlier comments that suggest that even when community consultation does occur with an adequate number of people, they don't seem to understand the process, how are you suggesting that that happen? Increased participation of the sponsor or a bigger role for the clinical investigator or perhaps some other mechanisms?

CHARLES CAIRNS: I think we were very interested, we are interested and remain so, in getting the feedback from the community consultation process back not only to the IRBs, but also to the investigators, potentially to sponsors, and even out to the public. So, not so much critical of the process itself in that piece of the information, but just to be sure that whatever information is gleaned from the consultation is also incorporated into this process and publicly available so that additional risks, for example, that might come out through community consultations can be incorporated into decision-making by the IRBs and additional safeguards performed. Or, for example, additional information could be publicized and put out in the public domain so that people realize that these questions and concerns were raised, see how these how these concerns were addressed by the investigator and the sponsor, and these are presumed protections that will ensue from their implementation. So, I hope I clarified that issue.

JEFFREY SHUREN: Other questions from the panel?
Thank you very much.

CHARLES CAIRNS: Thank you.

JEFFREY SHUREN: Next I call Dr. Rick Dutton, R. Adams Cowley Shock Trauma Center at University of Maryland Medical Center.

RICHARD DUTTON: Hopefully, this will work. Thank you very much. Welcome. Good morning, ladies and gentlemen. Thank you very much for inviting my comments.

Unlike the previous two speakers, I represent nobody but myself. I am a trauma anesthesiologist. I have worked at the Trauma Center up the road in Baltimore for the past 12 years. I have had an interest in saving lives in acute resuscitation in that time, and....

No. There we go. Was that you or me? Okay. I'll just ask then.

I've participated in many trials in emergency research, ranging from things that are fairly minimal risk as determined by my IRB, but nonetheless we can't get prospective informed consent for, to nationwide, multi-center, even international trials of pharmaceuticals or other products. You can see some of them listed here. I'm sure many of you know or are familiar with many of these trials. These are the ones we're trying to get done.

Next. This is where I work. This is the world's largest free-standing trauma center. This is the busiest trauma center in the United States. We take care of about 7500 patients a year. We have full-time research support. I have research nurses in the building all the time. We look at every patient coming in the door as a potential research trial subject because part of our mission, part of the University of Maryland's mission, as we have summarized it, "to heal, to teach, and to discover." And we're not trying to just to save the lives of our citizens, but everybody around the world as well.

Next. This is a patient. Marco Filiponi was a 17-year-old. He was injured one afternoon on a nice day. He was a perfectly innocent victim. He was hit by a drunk driver about 20 miles from this very auditorium. He suffered a significant brain injury when he hit his head on the B pillar. He underwent rapid-sequence intubation in the field because of his brain injury, a very controversial thing that we would like to study.

Next. Over the course of the ensuing weeks he was treated with a large number of therapies, many of which have

never been proven by an evidence base, many of which are accepted standards, some of which are beyond that, including decompressive craniotomy, decompressive laparotomy to control his intracranial pressure.

Next. He was in a coma for 37 days. He developed propofol infusion syndrome, which we didn't know about at the time. He became sick from that with multiple organ system failure requiring dialysis, requiring multiple Pressor infusions to support his blood pressure. He eventually underwent fasciotomies of most of his body to relieve rhabdomyolysis. He developed, at the end of this period, an exsanguinating coagulopathy, received more than 100 units of blood products over a couple of days, bleeding from multiple wounds, was treated with Factor 7 off-label and other investigational therapy. He eventually survived.

Next slide. I'm sorry. I think we missed one. And is intact, physically and mentally. He is a college senior at this point and doing very well. I have the pleasure of working in a center where we can take the kind of risks necessary to take care of a patient like this, where we can try new things, where we can go beyond what's

in the published literature, where we can stretch ourselves to save lives.

Next. The question is not just how do we do this, how do we learn to do this, but how can we bring this to other people? How can we take this to the rest of the world? How can we teach the rest of the country how to save lives in the same way? And, obviously, the answer is controlled research. We need--we end every paper we write with "Further research is needed" or "More study of this topic is needed." Many of these things, though, in emergency research are very difficult.

Next. Trauma is the fifth leading cause of death overall, fifth with a bullet, as we like to say. It is a rising cause of death. It is far and away the leading cause of lost productivity, lost income in the United States, and as we know from the global war on terror, this is going to be an increasing problem.

Next, and you can hit the button a couple times there.

Do any of us believe that we're not going to suffer another major terrorist event in the United States in

the near future?

Next. Terrorism is on the rise. Terrorism is a big concern. Mass casualty and emergency management of these patients is going to depend on good science and good medical practice.

Next. Unfortunately, trauma is a very chaotic environment, and caring for trauma patients and learning how to care for trauma patients better involves overcoming a number of obstacles.

Next. Trauma moves very quickly. You can't stop and have a discussion with a patient about a 20-page consent document if they're bleeding to death. That, by itself, would be unethical because we have stated, my predecessor, Dr. Cowley, the man for whom our center is named, coined the concept of the golden hour. And, while not getting into the science of that, the emotions of that are pretty clear. The faster you do things, the better patients do. And this our practice. This is how our center is built. This is how our practice is built because being able to move quickly in trauma cases is very important.

Next. Rapid-sequence intubation. This is a

patient intubated in my center within 5 minutes of arrival, not leaving a lot of time for discussions about research topics or much of anything else.

Next. This is a patient bleeding to death from a grade-5 liver injury. Again, this is a man who was injured in a motor vehicle crash, was in the operating room in the Trauma Center less than an hour later having emergency surgery. Again, not much time to get stuff organized. Yet, it's very clear from a lot of the work that we do, that the sooner therapies are applied, the better the patient is likely to do, and this produces one of the great difficulties in doing research in trauma. So, we want to apply the therapies early, but at the same time, we're very time-pressured to take care of the patient.

Next. Further, in Maryland, we see another problem. We have built a regionalized system of care. The sickest trauma patients in the state of Maryland, in fact in about a four-state area, come to the Shock Trauma Center. This is very good. We've demonstrated that this is a way to save lives in trauma care. Unfortunately, it means that the patient is moved a long way from where they live and the

community they're in.

Next. This is the Maryland Trauma Care System. As you can see, you can be 2 hours by automobile away from the Trauma Center, but only 20 minutes by helicopter, and we regularly see patients hours ahead of when we have family or other members of their community.

Next. The terminology is unclear, and I won't belabor this, because other speakers have spoken to these points. In terms of designing emergency research protocols, we have a very difficult time with some of these. I've had these conversations with my own IRB. I've had these conversations with members of the FDA. What constitutes clear benefit? What is a likely therapy to succeed? What makes a study easy or impossible to do?

And I will shed some light on that from our own experience. One problem we have had in trauma care recently is, if the study has to have a benefit, that's very often interpreted as a mortality benefit, saving lives, and that makes a certain amount of sense, except that many of the populations we're dealing with have a very low mortality with modern, consistent, rapidly presented trauma care,

which means you have to do very large studies to demonstrate a mortality benefit. And one of the things I will encourage the FDA to consider as they look at this going forward is the development of surrogate markers, whether it is amount of blood lost or functional status of brain injury patients, that can be used to make appropriately powered studies easier to do.

Next. We are conducting a trial now at the Trauma Center. This is a prospective observational trial, and it's simply what is our ability to get informed consent from patients? Because we do have research nurses 'round the clock, we can look at every trauma patient coming in the door. I don't have detailed data on this study yet. This is from my desktop computer as of yesterday afternoon when I put this together. But over the past 6 months, 2,011 patients were included in this study. You can see 43 percent of them arriving in the Trauma Center would have been unable to give consent for a study, and you can see the reasons why noted there, brain injury being the leading one, but intoxication, shock or hemodynamic instability, language barriers being the other.

Next. Of the 865 patients that we could not have gotten consent from, we asked the next question: When did their legally authorized representative show up? Could we have gotten consent from that person? And the answer is about 50-50. The biggest problem, as I already alluded to, is that in 3 hours many of our patients still don't have family available. So, this is not even the golden hour; this is 3 hours later, we still can't find a family member to talk to, and that's a very common problem. And then when the family does show up, there may be issues as well.

Next. Some other barriers we have. I believe that patients who have suffered a brain injury or patients who are in hemorrhagic shock really can't give consent for much of anything. I don't think you can have detailed discussions with those people, particularly not if it's interrupting the course of care. Having spoken to many families about research consent in these situations, it's an extremely difficult conversation to have. I usually start with something on the order of, you know, "We're here to take care of your family. You understand that we're always trying to find better ways to do that, that we do do

research and do studies here." Most people get that, and that helps frame the rest of the conversation, but even so, I may be time-limited. The family is certainly time-limited. They want to know what's going on.

And my impression of having these conversations early in the course of care in the patient, for instance, when they're still in the trauma resuscitation unit, early in the O.R., is it's very difficult to have this conversation without making it sound coercive. You know, "Your loved one's been horribly injured in an accident. We're struggling to save your lives. Would you like to participate in this research study?" And that's how it comes across to the family, and no matter how well you frame it, that's what they're hearing. That makes it extremely difficult.

Next. That's some of my personal experience. I'll be presumptuous and take a couple of minutes and make some recommendations for how I think this could work better.

Next. On the national level, I would love to have a, not just a coherent national policy, which I think is the whole purpose of this meeting, but also a national body to

do this. I think that the vast majority of people out here, the vast majority of the citizens don't really want to think about this. They want us to do what's right for them, and I know that's paternalistic, but I think very often that's true. When you take your car to the car dealer, you just want them to fix it. And a lot of people think about their health care that way and this kind of research issue that way.

I think that we should have a national IRB or national body that reviews requests for this kind of study.

I think it would allow for much greater consistency in application. I think it would provide a resource for the FDA, for the military, for the NIH, for other funding bodies to have a consistent policy around waiver of consent. I think that would be a tremendous help to the researchers. For those people in the population who do care about this, for those who are deeply concerned about the ethics of research, for those who are interested in and engaged in this, this would give them an avenue to express their concerns, and this would be a way to get those opinions collected. So, would these people be representing the

nation? Yes, in a way they would. I think that's probably the best way to get this done with the best ethical standards.

Next slide. And then personally, from the ground level up, my IRB--and I spoke to our IRB Chair before I came over today--he would like clearer guidance, obviously. He would like to know that he is in sync with the rest of the country about how we're processing these things.

I think, personally, that some sort of graded consent process or gradual consent is probably what's necessary, beginning with notification to the community that this is a hospital that conducts research studies, maybe a sign in your lobby that says, "We do research here. Ask if you have questions." And then working up. Initial notification to patients as you just heard suggested: "Can we put you in a research study?" or "We're doing research. Is that okay?" Without getting into the details in patients who have neither the time nor the capacity to deal with that. And then an ongoing discussion, and I think it's very clear that a good informed consent process, particularly for the complicated kinds of trials we're looking at now, needs

to be an ongoing process. It's not a single, one-time meeting, "sign this paper" thing. It's ongoing over a period of time, and you have to commit to doing that if you're going to do this well.

And then finally, as you've already heard suggested, I think when we do these kinds of studies, it's mandatory to evaluate them afterwards, even things as simple as we have done: calling back the patients who have been enrolled in one of these, after the fact, and saying, "Do you remember us talking to you about that study?" We've done this incidentally. About half the people say no. The half will go, "Yes, I remember you talking about it." We asked them, "Was that okay? Do you think that mechanism worked?" And the response to that has generally been very favorable. I haven't had anybody tell me after the fact "No, I don't like that." The most common response we get is "Thank you very much. Thank you for trying to do this better." And thank you for listening.

JEFFREY SHUREN: Questions from the panel?

SARA GOLDKIND: I'd like more clarification, if you would, on what you would see as a single national

policy. Would that be, is that beyond FDA guidance or?

RICHARD DUTTON: No, I think FDA is probably the right body to do this, and I'm happy to be here and participate in the discussion. I think that the simplest thing a national policy should say is, again, my own opinions, it should create a national board, whatever you call it, an IRB, to review this kind of study. It should make that kind of national-level review mandatory for people wanting to do this research, and it should provide clear guidance to the local IRBs for how to take something that is ethical and appropriate nationally and apply it on the local level.

DIANE MALONEY: I have a question, just picking up on the single national advisory board, and you talked about it as a national IRB, but you also talked about it I think in a different context as well. And so, I don't know if you were proposing alternatives, because an IRB makes decisions on go/no-go versus an advisory board could be one that just provides advice or recommendations that then a local IRB takes back and considers. So, were you proposing putting both of those forward or?

RICHARD DUTTON: I'm not sure exactly what the right legal structure would be. I'm not a lawyer, so I'm not probably qualified to say. I do think that you could handle this is a single national IRB. We heard earlier--51 studies in 10 years is not an overwhelming workload. This is still a relatively small area of research. I think that that national body would be advisory to the FDA, to the NIH, to other people considering funding studies or considering approval, but in terms of talking to the local IRB, what they would mostly be saying is, "We've looked at the study. It meets our requirements. It is appropriate. It is ethical based on our work. Let's find a way to get it done at the local level."

ROBERT TEMPLE: So, it sounds like this body would be some kind of hybrid, something like a central IRB, but better informed, wiser than what you expect, to the point where they'd have an appropriate body of ethicists and (indiscernible). So, it's a central body to review these things and then farm them out. Then the local IRBs would do their thing or defer to it, I guess is what your thought is.

RICHARD DUTTON: Correct.

ROBERT TEMPLE: If more of the effort became non-local, do you have any thoughts about what that means for community consultation? How do you do that if there's a national body?

RICHARD DUTTON: I think that's difficult, but personally, as potential victim, as we all are, I would like to think that my research rights were being protected by a group of people who are the best informed about the issues involved, both the science and the ethics, and who are the most interested. And one advantage of having a national body is it allows an avenue for people who are interested in this and do have strong opinions to present to get those forward. The problem, as you've heard, with community consultation is that most of the community is very hard to reach. There's a lot of other messages on their TV every day, and there's a lot of other stuff in their newspaper, and this is not something that most people want to think about.

I think that you still need the local IRB to be engaged in this because you may have particular cultural issues in certain communities, certain state laws or certain

local regulations that have to be fit into this as well. But that's the role, I think, of the local IRB, is to take a nationally approved trial and make it work in a particular community.

ROBERT TEMPLE: I guess my last question is it sounds like you really feel that exactly what "unable to give consent" means ought to be clarified more. I mean if you can sort of nod yes or no in a vague way, is that consent or what are the stages and grades of this? Which I don't think is really addressed by anything we've written so far.

RICHARD DUTTON: Well, I've thought about it quite a bit, and it applies in medicine generically. It's not just research studies. It's what can you get away with and what can't you. And I think most of us would say that it's appropriate on an individual level to be as conservative as you can. So, if, for instance, I say to a patient, "This is going to be a big operation. You may lose some blood. We may--we will transfuse you if that's necessary." "Okay." If there's any hint that they don't want that, that either requires a longer discussion or an absolute prohibition

against transfusion before we go ahead and do that. And I think that's how most of us would approach that sort of thing. Similarly, in the research, I can't have a long conversation at that moment, but if there's a suggestion from the patient that this is something they wouldn't want, then we wouldn't do it.

ROBERT TEMPLE: And presumably, although this isn't the forum for this, how much you try has something to do with how urgent the time of the intervention is. I mean our rule does have something about the therapeutic window, but exactly how to factor that in with how hard you try isn't terribly well specified.

RICHARD DUTTON: Exactly right. If you're bleeding to death and your unconscious, you're going to get transfused because we don't have time for that conversation.

If you're getting ready to have your aorta operated on electively, we can have a much longer conversation.

DENISE ZAVAGNO: I had a question about the statement you said a couple time, that you think most people want others to take care of this, sort of similar to when you take your car to the car dealership and you just want

them to fix it. But we have found, at the FDA, that there are some people who feel very strongly about emergency research without informed consent, and they want to have some input, and they want to know that they might be involved in a clinical trial. If we moved the way we evaluated research to this national advisory committee and they live in Oregon and the meetings are here in Washington, D.C., or Rockville, Maryland, how would you deal with that?

Would you give people an opt-out mechanism or recommend that we have opt-out mechanisms to handle those individuals who feel very strongly about emergency research?

RICHARD DUTTON: I agree. I think having this done on a national level actually improves people's access to it. It makes it a higher profile, and makes it an obvious "where to go," if you have a concern about this. I agreed very much with the statements we heard before, that this kind of trial should be publicly available. I should be able to go to a government Web site and look up what are the provisions of this trial.

I think that opt-out is important. I think we will need some kind of opt-out mechanism going forward.

Maybe my driver's license needs to say, "Yes, organ donor. No, research subject" on it. But I think that would be a lot--that's sort of opt-out would be a lot easier to manage nationally than locally.

JEFFREY SHUREN: Other questions? I have one question. There's been a recurrent theme today about conducting follow-up evaluations to kind of look at the success or failures of processes we've put in place, and you've talked about studies you're currently in the middle of conducting. Maybe there are others you have already conducted. Are there particular validated outcome measures or benchmarks we should be taking into consideration as we move forward?

RICHARD DUTTON: It's very hard to say what population, what percent of the population should accept a study before it's acceptable. I don't know legally or ethically if that's how you would want to approach that kind of thing. I think the best advantage you get from post-hoc screening, from asking your patients afterwards "What did you think of this mechanism?" is the individual statements you get back, of this was good, this was bad, "I liked

this," "I didn't like this." And, again, having a learned national body who can take that kind of feedback and do something with it would be very helpful.

JEFFREY SHUREN: Thank you.

RICHARD DUTTON: Thank you.

JEFFREY SHUREN: Next I'd like to call Dr. Henry Halperin, American Heart Association's Emergency Cardiac Care Committee.

HENRY HALPERIN: Thank you for the opportunity to speak here. On behalf of the American Heart Association and over 22 million American Heart Association volunteers and supporters, we would like to offer the following comments at the Food and Drug Administration's hearing on conduct of emergency clinical research.

Since 1924, the American Heart Association has dedicated itself to reducing disability and death from cardiovascular disease and stroke, the number 1 and number 3 leading causes of death in the United States, through research, education, community-based programs, and advocacy.

American Heart Association efforts include, but are not limited to, the following: the development of evidence-

based clinical practice guidelines designed to help advise physicians and other providers on the prevention, treatment, and chronic management of cardiovascular disease and stroke, the development of international guidelines for emergency cardiovascular care in collaboration with the International Liaison Committee on Resuscitation, and the development of a series of high-quality courses and training materials that serve to educate the public on how to recognize the signs of heart attack and stroke, how to administer cardiopulmonary resuscitation, and instruction on proper operation of an automated external defibrillator.

Approximately 250,000 people die annually from sudden cardiac arrest outside of the hospital. Central to our efforts in improving outcome of sudden cardiac arrest is our commitment to ensuring that clinical research in this critical area proceeds and that the research findings are translated into practice in an appropriate and timely manner.

There are a number of barriers to the conduct of this research, and that is the reason for our presence here today. I would like to comment specifically about the issue

of community consultation and public disclosure, informed consent in resuscitation research, and I've submitted a draft document that is in development by the American Heart Association. This document is not yet in final form and may be modified before publication, but there are a number of concepts included within in it about which there is general agreement within the resuscitation community, and it is these that are the substance of my testimony today.

So, we feel that in the current guidelines, the current limitations include that there are substantial delays in obtaining approval for research study using the emergency exception process. Each institutional review board may lack experience in determining what types of community consultation and public disclosure are necessary.

There's ambiguity in the regulations as to how individual IRBs should implement such community consultation and public disclosure.

Next slide, please. So then the objective of our work is to provide guidance for implementation of community consultation and public disclosure.

Next. We've developed a template which provides

for quantification of the minimum requirements that an IRB might adopt. The template gives examples to help IRBs quickly become familiar with the process of implementing and reviewing studies proposed with exception to informed consent, and the template proposes the trials of interventions approved by the FDA for the indication being studied should require different levels of community consultation and public disclosure than studies of unapproved interventions.

Next. So then the ethical guiding principle is, is that there are a range of actions that are acceptable to protect subjects' autonomy dependent on the risk of the study, and the risk referred to here is the incremental risk of participating in the proposed study over and above the risks of having sustained a life-threatening emergency and being treated with standard interventions. The higher the risk of the study, the more stringent are the actions that are required to protect subjects' autonomy.

Next, please. A trial of an approved therapy should not require the same level of community notification and consultation as one where non-approved or not-generally-

accepted interventions are being introduced for the first time. For interventions that were not approved by the FDA, the risk of the study could be incrementally higher, and the level of community consultation and public disclosure for the study should similarly be higher.

Next. We propose, then, that it is ethically acceptable to stratify the intensity of community consultation and public disclosure based upon the anticipated incremental risk to subjects of participating in a research study. We acknowledge that any research study may have unanticipated risks, but we base our argument for stratifying community consultation and public disclosure on the reasonable and prudent prediction of subject risk.

So then, for stratifying community consultation and public disclosure, we feel it's analogous to how IRBs currently review research protocols and informed consent documents. For example, IRB review of a protocol that studies anonymous serum samples will not require the same considerations as a project involving the use of a surgically implanted resuscitation device. The study of anonymous serum samples may be considered to have minimal

risk and therefore be eligible for expedited review, while the implanted device study requires standard IRB review.

So then, for stratification of risk, the template breaks studies into minimal, low, intermediate, and high incremental risk. Instead of paying heed only to the inherent risk of the underlying disease, which is present whether the patient is enrolled in the study or not, we recommend evaluating the incremental risk from participating in the proposed study. That evaluation can then be used to determine the degree of community consultation and public disclosure appropriate for the proposed study.

So then this is the template for assessment of incremental risk of being in a study. And it's probably difficult to read that, but a copy of this is actually included in the written comments so that it will be clearer what's on the template.

So, basically, the left column is the study type, and it breaks this assessment into whether devices and intervention are diagnostic, and then the minimal-, low-, intermediate-, and high-risk categories then have different considerations for whether to put them into those

categories. And then the IRB could potentially use this information, which are assessments that I'll get into in the next few slides, to decide then which category it fits into.

And then the bottom row is the community's potential sensitivity, which is an independent factor. If a community might be particularly sensitive to one particular kind of intervention, that actually might rise the incremental risk applied for the study, and then that would increase the level of considerations and community consultation and public disclosure that may be needed.

Next slide. So then this is a similar template for suggesting community consultation and public disclosure at different incremental risks. And so, once the study is determined to be minimal, low, intermediate, or high incremental risk, then different levels of community consultation and public disclosure then can be applied based on these considerations. And I have some specific examples on the next few slides. And for patient/family notification of participation, we do feel that reasonable attempts for written communication, regardless of patient survival status, should be applied.

Next slide. So then, as an example from the template, minimal risk for a therapy would be if there was FDA-approved for the proposed study indication and/or already in clinical use for the study indication, and have minimal incremental risk of harm from being in the study. And this means that randomization does not introduce any significant delay, and there's no loss of privacy on review of the data. In addition, it should be true that it's very unlikely that there's sensitivity in the community for doing this particular study. An example of this would be an approved mechanical CPR device versus standard therapy, where the mechanical device is approved for the study indication. So then, again, the only incremental risk of being in the study is, does randomization impart a delay in applying the device and is there any loss of privacy? If those two factors can be mitigated, then it really is a minimal risk study. And also, amiodarone versus lidocaine would be another example.

Next slide. So then, for a diagnostic to have minimal risk, it should be non-invasive and not used for real-time clinical decisions and very unlikely to have

community sensitivity. So, an example of this would be a non-invasive monitor and a low-volume blood drawing, where data was collected and that was not used as part of the therapeutic decision-making.

So then low risk for a therapy would be something that was FDA-approved for the proposed study indication and/or already in clinical use for the study indication, but there is a higher than minimal risk of harm from being in the study and very unlikely to have community sensitivity. And this would be a situation where in fact the act of randomization might actually cause a little bit of a delay in applying the device, so that there may be some slightly higher risk for the patient being in the study.

Next slide. So then the suggested community consultation and public disclosure for the low risk study would be for community consultation, review and feedback from an appropriate group representative of the study community, or alternatively, we can consider a solicitation through a Web site or public notices, such as a mass media piece with a call-in number and/or Web address for feedback.

And then, for the public disclosure, it could consist, in

this low-risk situation, to be a single targeted effort most likely to reach the study community, such as a mass media piece or distribution of information in a more focused manner to likely subjects. This actually comes from real-world examples where, say, a particular minority group or senior area might be the subject of that study, and that particular area then should be targeted. So then that could be targeted with a poster, a brochure, or newsletter article in a senior citizen center where the study would be conducted. And then, for patient or family notification, we would recommend that there would be reasonable written attempts.

And the template goes through similar considerations for intermediate- and high-risk studies, again increasing the amount and types of community consultation and public disclosure required, or at least recommended.

So then, a manuscript has been commissioned to be considered as an American Heart Association scientific statement. That manuscript is under review and it's still in evolution, but we did include a draft of that. The

Emergency Cardiac Care Committee of AHA has created a Web site, and it's hard to see, but it's www.americanheart.org/emergencyexception. And this is proposed as a repository of information for IRBs. This Web site is up and running, and it does have sample public disclosures and sample community consultation. We're hoping this information will supplement and add to information that is available from the FDA.

So then, in conclusion, we would respectfully hope that these recommendations could be seriously considered for implementation into the final guidelines, and we thank the agency for this opportunity to participate in this discussion.

JEFFREY SHUREN: Thank you. Catherine?

CATHERINE LORRAINE: Hi. I was wondering if you could comment on something for me. This is quite a finely graded system that you're proposing IRBs would apply in reviewing this kind of research, and we've heard from previous speakers that there is not uniform understanding of these regulations or comfort with the requirements of this research, among IRBs. And I'm wondering if you've thought

about how IRBs might actually be educated about such an approach or whether you think it might be the purview of a national body, which has also been alluded to?

HENRY HALPERIN: Well, certainly the national body has, you know, certain advantages for uniformity, but--and I think Dr. Weisfeldt will talk about that a lot more further on, but dealing with the local issues, you know, would be more difficult for the national IRB to deal with. From our own experience at the American Heart Association, actually having a number of members who have actually participated in a lot of these studies, a lot of them actually had input into this document, and a lot of this is based on experience from dealing with IRBs.

And the education process seems to be a major issue here. The first time through for an IRB, they really have no idea what, you know, what community consultation and public disclosure really means, and what types and kinds of community consultation and public disclosure are actually needed in one particular study. So, there's a lot of, you know, doubt in their minds and they're trying to figure out how do they deal with this.

And what we're proposing in this work is, although it is finely graded, I think there are real distinctions among these different levels of minimal, low, intermediate, and high, where they could actually use concrete criteria and actually read through this and actually decide, you know, is this a low-risk study or a high-risk study, and therefore, you know, use the examples that we provide or whatever other information they feel is appropriate for their own situation in order to do it. But we're proposing this as kind of a guideline to jump-start the process for IRBs, and it would mainly be probably newer IRBs, because some IRBs have gone through this process and have been educated and have dealt with the FDA a lot and are really getting on board, but those are really the exception. We're trying to make this a lot more generally applicable by giving concrete criteria for how to deal with these issues.

SARA GOLDKIND: I'd like to just explore a little bit more the section that you have on communities' potential sensitivities. So that would be the IRB, if I understand you correctly, the local IRB making an a priori determination of the sensitivity level for the community?

HENRY HALPERIN: That--it certainly would start with that. There have been some studies where a community representative on the IRB might be asked this particular issue, you know, what are the local political, cultural, social issues in this community? And in a few situations, it's been really made crystal clear to the IRB that there is certain sensitivity among, you know, in a particular group.

And, I mean, the IRB may not know about these things, but I think it probably is incumbent upon the IRB to understand the make-up of the community at risk, and if there are potential cultural, ethnic, social sensitivities that might be there because of their particular population that's there, then they actually should seek out representatives of that community in order to at least have some, like, you know, maybe reverends or Indian leaders or something like that, in order to see what that particular community where the study may be done, you know, what particular sensitivities they may have for this.

SARA GOLDKIND: So, given this model, do you see a role for a centralized IRB for multinational, for multi-site studies, or do you think that this model best applies to

single, you know, institutional IRBs?

HENRY HALPERIN: Well, I think it's probably more for institutional IRBs, but certainly it would be nice if there actually were, in fact, concrete criteria for a national body as well as local bodies, so there was actually some degree of uniformity, at least how the regulations were assessed and implemented, even though there may be, you know, community differences that the regulations now want to happen. I think those could be done readily by the local community, but it would be, you know, one possibility that in fact a national board would use similar criteria so that in fact the criteria are uniform among all these different bodies, but yet the specifics that come out may be tailored to a particular community, even though they're using common criteria.

SARA GOLDKIND: Thank you.

JEFFREY SHUREN: Other questions from the panel?

Thank you very much. Next I'd like to call Dr. Ronald Maio of Pediatric Emergency Care Applied Research Network.

RONALD MAIO: Thank you. Emergency research is

complicated by the need to balance patient autonomy while conducting the research needed to improve patient care. The Pediatric Emergency Care Applied Research Network, known as PECARN, was organized in 2001 with the goal of conducting high-quality, scientifically rigorous research in pediatric emergency care. We are currently involved in a study that will utilize the exception from informed consent. We applaud the FDA in publishing the July 2006 guidance and providing the opportunity for public comment. The guidance provides greater clarity to the process of obtaining an exception from informed consent under 21 CFR 50.24. We thank the FDA for an opportunity to comment on those portions of the guidance where we believe further clarity or change is needed.

First, we agree with the comments from our colleagues from the Neurological Emergencies Treatment Trials, NETT, and the Resuscitation Outcomes Research, ROC, networks and will not repeat their cogent arguments contained in their submitted abstract. We will instead focus on areas that have not been addressed or require pediatric input.

Neither the regulation itself nor the 2006 guidance recognize the personal loss of autonomy that is inherent in every emergency encounter. While the research community has begun to understand the concept of incremental risk, that is, additional risk associated with performing a research study, we believe that we also need to begin to incorporate the concept of incremental loss of autonomy. This is the additional loss of autonomy associated with research.

In general, patients in emergency situations do not have personal autonomy. They do not have the luxury of discussing clinical treatment options with their physicians, nor do their family members. There is simply not enough time to have these discussions. Patients and their families trust that their emergency physician will provide the best care available, but what if that best care is unknown?

As a nation, we are faced with an ethical choice: We can choose to allow every emergency encounter to be an uncontrolled experiment at the hands of the individual physician, and hence fail to advance the science, or we can choose to enroll patients in a systematic manner into

rigorously controlled clinical trials with regulated treatment arms and safety monitoring aimed at determining the best treatment outcomes.

The former approach, caused in part by the difficulties in implementing this type of research, has been described ethically as follows: "As the treating doctor, you are free to do whatever you want as long as you promise not to learn anything." The latter approach is more ethical because it maximizes the likelihood of benefit for not only the individual patient, but also to society.

The take-home point is this: Well-conducted emergency research itself poses no additional loss of autonomy beyond that of standard care. What this research does do is (1) ensure the highest quality of care by requiring the most intense level of scientific review, and (2) provide safety monitoring above that of normal clinical care, and finally (3) ensure that we can improve the care of patients to the maximum extent possible.

We believe that the use of the term "life-threatening condition" is restrictive in that it precludes study of conditions that are not immediately life-

threatening but have significant morbidity. Pediatric emergencies are rarely life-threatening, but may have the potential for serious long-term morbidity, and there is little research to determine optimal treatments in the emergency setting. Surely, loss of limb or loss of vision or loss neurological function, for example, deserve the same benefits of carefully controlled research as loss of life. We believe that the regulation should be aimed at emergency conditions, that is, conditions that must be addressed immediately and without the delays inherent in a meaningful discussion about informed consent.

The guidance is not clear about what constitutes "unsatisfactory or unproven therapies." The term "unsatisfactory" is meaningless unless it is placed in the context of the question "unsatisfactory" compared to what? We believe that the threshold test for allowing study under the exception should be clinical equipoise, that is, the preponderance of evidence to date suggests that the two treatments are equal, but there is a suggestion that a new treatment may be better.

For example, current survival rates for out-of-

hospital pediatric cardiac arrest are approximately 5 percent with epinephrine. Is that satisfactory? It is compared to placebo, but what if a new medication shows promise in animals? Why should we accept 5 percent survival when the new therapy might provide 8 percent survival? Then we would argue that epinephrine is unsatisfactory.

What if survival for near-fatal asthma, for example, is 70 percent with current therapy, but animal studies suggest 80 percent survival for a new medication? We believe that, in this context, the status quo of 70 percent survival is unsatisfactory.

We believe that the exception should be allowed whenever there is clinical equipoise and therefore the direct prospect of improving the care of patients.

Definition of community. The guidance implies that community consultation should attempt to include both the geographic population from which the subjects will be drawn as well as the subjects who have the disease of interest. Prior studies utilizing the exception have shown that many methods of consultation with the general community, such as public meetings, have not been effective

in achieving the bi-directional input that is intended in the spirit of these guidelines.

We believe that targeted and focused community consultation should occur in groups who are vested in the study, such as community leaders or patients who have the disease, to obtain meaningful input, particularly for pediatric studies. Parents are constantly bombarded with information about potential diseases or concern for their children. Messages regarding one particular study will not receive their attention if their child does not suffer from that particular disease. People, in general, cannot relate to the abstract; it is only when such research is relevant to them personally or is relevant to their constituents that we will achieve meaningful input.

The guidance does not provide IRBs with input on what to do with negative community input. Although the spirit of the guidance suggests that IRBs need to take community input into account, the message may be perceived as a need to obtain community consent.

Special Populations: Children. We believe that the guidance should be more explicit about the applicability

of the regulations to trials involving children. There may be an assumption that children are more vulnerable under resuscitation circumstances than adults. In truth, all patients in a life-threatening situation are equally vulnerable. Excluding children on this basis would be unjust. In addition, many assume that children automatically have a parent or guardian who can decide on research participation. This is not often the case in the emergency department, as children often present with school personnel or babysitters. Even when parents or other family members are present, the emotional distress experienced during a medical crisis precludes meaningful discussion about informed consent during the therapeutic window.

Finally, opportunity to object. Finally, we would like to applaud the FDA on its emphasis of the need to provide opportunities for family members or patients to object to their participation in clinical research protocols. Despite the arguments we have made in favor of emergency research, we recognize the tainted history of research in the United States and the fundamental distrust that some communities have in our medical system. By

providing families and patients several options for refusing participation, we go a long way in restoring this trust and ensuring that future generations can reap the benefits of participation in clinical research trials. Thank you.

JEFFREY SHUREN: Thank you. Sara?

SARA GOLDKIND: I'd like to explore a little bit more with you your comments on community consultation, and I understand what you were saying, that it should include groups who have a vested interest in the study. However, there are many circumstances, many conditions that, you know, emergency conditions where there is no easily identifiable community, if you will, who have a vested interest in the study--you know, trauma victims in a car accident. We're all that vested. We're all that community.

All of us make up that community. So, do you have any thoughts on how you might approach community consultation for such emergency conditions where any of us could make up that community?

RONALD MAIO: That's an excellent question. I think that in those cases--basically, I think we have to start from what is the population that we're trying to

approach. And if it is the general population, for instance, something like trauma in a pediatric population, then I think we need a more general approach, but for something, for example, for seizures, it's possible that you could do a little bit more honed-down view because, in fact, a lot of kids that come into the emergency department that do have seizures have a history of seizures. Granted there is a small group that doesn't, and we would want to address that in some way, but I think we could be more focused and more selective, and not just have, you know, one flavor, a vanilla for everything.

JOANNE LESS: You had mentioned in the beginning of your comments that you're currently involved in a trial, and I was just wondering if you could give us some examples of the community consultation that went on at your institution, especially if your study does include pediatrics, and some of maybe the additional consultation or focusing that you did to take into account that patient population.

RONALD MAIO: Well, this trial, or the portion of the trial that's going to invoke the exception has not yet

begun, and we are actually putting that together. We are currently approaching the IRBs from the different sites to discuss with them how we might go about with this process. So, I can't really tell you how we did it because we're in the process of crystalizing that right now.

DENISE ZAVAGNO: I had a question about your discussion about the term "unsatisfactory." You--I think I heard you say that it might be enough that the new treatment provides just a little bit more benefit. My question to you then is, would you have us use a different term than "unsatisfactory"? Is there another term that you think captures the threshold that we should use when evaluating whether or not a specific treatment could be used in an emergency trial?

RONALD MAIO: You know, I have to be honest with you, I haven't thought much about a new term. I've just thought about the fact that we need to be open to what we consider unsatisfactory to be, and I think sometimes you could argue for certain situations that, even if an intervention is going to increase survival or decrease morbidity by 1 percent, it might be worth it. Other times

you might argue that, you know, if we don't get to 5 percent or something, it's not worth it. But I think the point is that we really have to be open about our concept of what do we mean about "unsatisfactory." Here, again, I don't think you can just pick one number and say, well, if it's not 10 percent, then you can't do it. I just don't think we can take that approach.

CATHERINE LORRAINE: I would like to ask you a question about the regulation generally as it applies to pediatric research, and I'm wondering, in your experience, if you find that there are, aside from the issues that you've raised, whether there are other aspects of the rule that don't fit pediatric research very well, or whether in general it does fit pediatric populations as well as adults?

RONALD MAIO: I think that the basic elements that are in the rule do, but I think where it falls down--and I've made comments to this and it's also in our written comments--is this idea of children being an especially vulnerable population, and I think that, on one hand, yes, they are, but when you're talking about emergency situations in particular, if you're talking about a child that's in

extremis, that is unconscious, I think, I would say they're just as vulnerable as an adult in that situation. I think that's what we have to understand because I think there's this visceral feeling, you know, that all of sudden, when you want to do this with children, the reflex is "No, we can't do it." But I think that when we step back and we look at it in a, you know, a thoughtful and logical way, I don't think that they're any more vulnerable than adults. I mean that's my personal opinion, and I've practiced as, I'm a general emergency physician, and I've taken care of adults, and I've taken care of children too, that have been in extremis. So, that's my viewpoint on it.

MICHAEL CAROME: Just to clarify regarding discussion of "unsatisfactory," your comments seem to propose perhaps removing that as a requirement and substituting the concept of "equipoise." Is that a correct interpretation of your comments?

RONALD MAIO: Yes, it is.

MICHAEL CAROME: Thank you.

DIANE MALONEY: I had a question, just wanted to go back to the community consultation just from a practical

standpoint. How helpful would it be for sponsors to provide information, if it's a multi-center trial, to each of the sites? And how much does one site pay attention to what another site is doing in terms of the variability, in terms of the detail that might be provided in various communities?

RONALD MAIO: I think it would be very helpful.

For instance, in my own case, I happen to be the Director of the Office of Human Research Compliance Review for the University of Michigan, and we are in the process now of putting together procedures so we can do this type of research in emergency medicine because we think it's important. It was very important for the IRBs and the other administrators at the university to see what was being done at other places, how to operationalize this. So, I think, to answer your question, I think it would be very valuable to get this information, but, once again, I think you have to have flexibility because every place is going to be a little different. But I think the more examples you have to work with, the better, and I know that that's one thing that our IRB really liked to see.

JEFFREY SHUREN: Other questions? One final

question regarding community consultation. We do talk a lot about trying to hear from those individuals with a particular condition who might be subject to an emergency research clinical trial. In this day and age, there are many patient groups representing individuals who have various conditions, some of them that may be life-threatening. To what extent should we consider those groups either as surrogates or complementary to engaging local communities for input?

RONALD MAIO: I guess I would say that I would definitely see them as complementary, but I wouldn't say they serve as a surrogate for the community, and I guess that's my viewpoint on it.

JEFFREY SHUREN: All right. Thank you. It is now 10:25. We had planned to take a break at 10:30, so why don't we take a break a few minutes early? And I will ask everyone to reconvene at 10:40, rather than at 10:45. So at 10:40, and we'll pick up there.

(Break)

JEFFREY SHUREN: And let me ask everyone to take their seats.

We're going to go just slightly out of order, just due to a scheduling conflict. So, I'd next like to ask Dr. Myron Weisfeldt, Johns Hopkins University School of Medicine, to come forward.

MYRON WEISFELDT: Yes, thank you very much for allowing me to address the panel, and particularly to deal with my timing problem. I am the Chairman of the Department of Medicine at Hopkins. I've been involved in clinical research for a lengthy period of time. Dr. Temple will remember that we did the pivotal study on TPA that got the FDA to approve that in acute myocardial infarction. I worked with a group at Hopkins and led the group that led to the first implantation of an automatic implantable defibrillator in a human being, and those efforts that resulted in significant patient survival led to ideas like the AED project and, in fact, I did obtain the IDE for the PAD study from the FDA, but it was only when we were ready to start the study, I called the FDA to say that we were going to activate our IDE, and I was told that we actually didn't need an IDE for the study. So, it was an interesting episode.

My plea is really a reflection of some comments of Dr. Biros and Dr. Halperin, which deals with the desirability of a national advisory board or national IRB for this type of research. I don't want to repeat or read a written statement, but I would rather comment to the substance of the issue more informally because I think the formal issues have really already been stated.

The first issue is that the bar for IRBs for this kind of research is very high. Appropriate animal and other preclinical studies must support the potential of the intervention to provide direct benefit, and the risks associated with the investigations are reasonable in relationship to what is known. Those are very high standards for IRBs to do. And the ROC consortium, which Dr. Ornato and Dr. Minei will describe, because of the breadth and depth of the study, will deal with 200 IRBs that are individually responsible for making this judgment. And we see within this network already the formulation of at least regional IRBs for exactly the purpose that we are talking about, that in these communities, the academic IRB, with better expertise, better knowledge, is looked upon by local

IRBs as a reference IRB.

But where we come to proposed studies, where really very difficult value judgments will have to be made, and I'm going to mention two because they are studies that are on the agenda of ROC consideration in CPR research, and those are the use of beta blockers in patients who have cardiac arrest and resuscitation. There are animal studies that show that beta blockers are beneficial. There are animal studies that show no benefit. There are theoretical reasons to think that use of a beta blocker may be harmful, particularly after the period of resuscitation. So, there's a very difficult value judgment that needs to be made.

Another potential study is the administration of erythropoietin versus placebo in the arrest victim. There's much in the mechanistic literature to suggest that this agent may be beneficial. There are some concerns about prothrombotic complications of erythropoietin, particularly when the blood count goes up or the hemoglobin goes up. And there are some pilot studies suggesting in man that this agent might be beneficial in stroke, and in animal models it's very clear that the agent appears to be beneficial in

stroke and in acute myocardial infarction in experimental animals. So, you have examples here of the real-world possibilities of important studies that we could do, where this kind of value judgment would be very difficult for individual IRBs throughout the community to make.

The proposal for a national advisory body or a national IRB is not intended to take the place in any way from any of the provisions that at least I have in my mind for this advisory board versus the local IRB community consent and community information. It is directed significantly at the issue of the quality of the judgment that needs to be made in this very sensitive area of research and very difficult area.

I would remind you that in out-of-hospital resuscitation, in trauma, and in CPR, we are dealing with populations in which the survival is 10 percent in CPR, and in severe traumatic injury, the survival rate is 40 to 60 percent. So, when you are approaching the family, as you must do and should do, with regard to their inclusion in research, in the CPR arena 90 percent of those family members will be told that their loved one, without their

consent, participated in research that was approved by a local IRB, and that notion is terribly intimidating in fact to the doing of research by local IRBs from the point of view of litigation. And this is, that issue is particularly true for small studies of the practice of research that might go on in individual centers of research as preludes, if you will, Phase 1/Phase 2 studies to, more broadly, Phase 3 studies where outcomes might be definitively decided on the basis of small pilot studies in a local environment.

There is always concern in every setting about the expertise of the individuals and the conflict of interest issues. And I believe that the advisory committees of the FDA and the advisory committees to the NIH that are appointed on the basis of the criteria that we have for such appointments are the best that this society and this country have been able to generate from the point of view of knowledge and understanding and freedom from conflict of interest. And the government having a significant role in the appointing of such individuals, I believe, enhances the credibility, the integrity, and the desirability of the process of assessment.

I think in the public arena there are a lot of comments that are worthy of attention about how panel members and advisory members are appointed, but I do believe that the attempts and the efforts that are being made in these two bodies, the NIH and the FDA, are probably the best that one could imagine for identifying individuals with knowledge and expertise and freedom from conflict of interest.

I have only--and therefore, I don't want to be doctrinaire about whether this body should be mandatory or advisory. I think, if it is created, it will become usual practice, and therefore I do not think it matters. And I think the example that makes the point is the recombinant gene therapy issue. It's where for many years we had an advisory committee on recombinant gene therapy where major studies and all studies needed to go, and that committee, historically, was disbanded and then, when a difficulty occurred in this arena, that body was reestablished in an effort to provide reassurance to the public about safety of that particular aspect of clinical research.

A final final point, that the regulations and

approach, which I am profoundly in general support of, do not provide any guidance as to what to do with community input that is significantly adverse to the performance of the study. Yes, we can exclude or try to exclude people who object to the study by wearing paraphernalia that might identify them as objecting to individual participation, but if there is an objection in general to the performance of such studies or the specific details of a specific study, it is very hard to identify what guidelines would be used as to what should be done with adverse community input.

A reference national IRB, with a Web site, with comments that come in on a national level, with a Web site that is responsive, could not only provide the answer to that particular question, but obviously, when similar questions came up at other IRBs, a reference to that protocol, that question, that answer, could be available for use by the local IRB.

So, I believe it is not only the science and the integrity and the judgment about appropriateness that might be enhanced by this type of body, but I believe this body would be frequently consulted by the local IRBs with regard

to the community consultation issue as well as the issue of the appropriateness of the Phase 1/Phase 2 local study, where it is very difficult for a local IRB to make a judgment.

I'll conclude by just an example. Although I've been involved in the kind of Phase 1/Phase 2 studies, again, through the majority of my career, when I was at Columbia University we looked at the literature and got interested for a lot of theoretical reasons in how good it would be to put the patient, during CPR, in a prone position rather than supine position and to press on the back, because there were a lot of theoretical reasons why that might be better and there were some pilot studies without controls that suggested that reasonable perfusion could be obtained. It took 4 years and an ultimate judgment of minimal risk that ultimately got the approval to do a study in which, at the end of failed resuscitation, we would put the patient from their back on their stomach and then put them back on their back again and, just for 2 minutes, would measure the arterial blood pressure in those two positions. It wasn't an overwhelmingly successful study; it wasn't a detrimental

study. But the 4-year delay was quite remarkable in terms of being able to do this. If we had a national IRB, I think that that kind of delay, that kind of anxiety about, of local IRBs over approving, if you will, adventuresome studies that have reason would certainly be enhanced.

So, again, I appreciate the opportunity to speak to the group and would be happy to answer further questions.

JEFFREY SHUREN: Thank you. Questions from the panel?

ROBERT TEMPLE: This national body you think should report to whom, exactly? Is it an FDA body, an OHRP body, an NIH body, an independent private body, or doesn't that matter?

MYRON WEISFELDT: In the ongoing studies that we are doing in the Resuscitation Outcomes Consortium, I see a lot of communication and a lot of collegiality in the relationship between NIH and FDA, and whether this could be a body that would have joint reporting or whether it should report to one or the other and be available to the other agency, I think that's a governmental issue. But I see the two having a stake, very significant stake, in this issue.

JEFFREY SHUREN: Well, along those lines, you had talked about the FDA advisory committees, the standards that we use. In selecting members for this national body, rules for operation, are you suggesting that we use the same regulations, the same requirements and standards that we currently use for the FDA advisory committee? And, if so, do you think that there should be any additional tweaks to that in the setting for this particular entity?

MYRON WEISFELDT: I have on one occasion served on an FDA advisory committee on CPR, and I thought that the criteria and standards that were used--there were some of the members of the panel that were allowed to be present but not to make a judgment or a vote because of conflict of interest--I really thought the entire FDA process was commendable and was a high standard, and I think that standard would be excellent for this purpose.

CATHERINE LORRAINE: I would like to ask you to elaborate a little bit about the expertise that you would like to see represented on a national board.

MYRON WEISFELDT: Yes.

CATHERINE LORRAINE: Particularly in light of your

comment that this kind of board could supply some help to local IRBs on issues of sensitivity in communities and particularly negative attitudes.

MYRON WEISFELDT: I would think this body should have broad, rather than narrow, representation, but clearly a significant component of scientific--a scientific body capable--and the majority, I think, should be of a scientific nature in emergency medicine, but I think that ethics, legal, community input, as are on IRBs, would be very important to be part of this body.

JEFFREY SHUREN: Other questions?

DIANE MALONEY: I just also wanted to ask, because, again, I've heard a lot of people talk about a national IRB or a national advisory board, or something national. And, to me, an IRB is one thing, and, you know, there are regulations that describe what an IRB--what the make-up is, what an IRB does. FDA does have advisory committees as does NIH, you know, the RAC that you mentioned on gene therapy, and they are not IRBs. So, I don't know if--could you comment on your take on, is it important that this body actually be a national IRB or that there just be

some sort of national body that could provide advice on scientific and ethical issues?

MYRON WEISFELDT: In my written comments here, I've deliberately demurred from making a judgment on that issue, and I'm going to continue to not respond. I do not believe it is important as to whether it is in fact advisory or IRB specifically designated. I think the existence of either, on the basis of what we've discussed, would be a step in the right direction.

JOANNE LESS: Can I ask a question? You had mentioned that you had served on some of our FDA advisory committees, and I was just wondering, would you see, instead of having a national advisory board, if we just took all of these studies that came in to us to our advisory committees?

Because currently we do not take too many INDs or IDEs--at least IDEs, I don't know about INDs--to our advisory committees unless there's particular issues. And would that serve the same purpose? Or do you see an advantage or disadvantage?

MYRON WEISFELDT: I believe that the panels at the FDA have a specific regulatory requirement and objective,

and those differ, in my opinion, from the goals and objectives and the perception of the public, that the public would have about an advisory committee or a national IRB. I think they're differential, you know. I think you could do this with expanding or changing the mission, but of course that is isn't then an advisory panel. The constituting of the FDA is for the safety and efficacy of drugs and devices. That's specific, that is, yes, you promulgated these regulations. We understand you are involved deeply in the enforcement and the quality controlling of those issues, but the role that an advisory committee could have in the context of what I'm talking about is different.

JEFFREY SHUREN: Thank you.

MYRON WEISFELDT: It was a pleasure.

JEFFREY SHUREN: Next I'd like to call Dr. Robert Nelson of Children's Hospital, Philadelphia.

ROBERT NELSON: Thank you and good morning. Just by way of introduction, I'm a critical care physician in pediatrics at Children's Hospital in Philadelphia. I should say, as part of the full disclosure, starting next week, I'll actually be joining FDA in the Office of Pediatric

Therapeutics under an IPA as their pediatric research ethicist, but I'll still be keeping my faculty appointment and my academic and research activities and job at University of Pennsylvania. So, it occurred to me this may be the last time, at least for a while, that I can officially advise the federal government. (Laughter)

So, although I'm speaking for myself, my comments are informed by the work that I've conducted over the past 2 years with my colleagues, Nancy King of the University of North Carolina and Ken Kipnis of the University of Hawaii. Together, we will be submitting written comments that will address the questions in more detail by the November 27th deadline.

I and my colleagues are supportive of the concept of research conducted under an exception from informed consent, but remain concerned that a lack of clarity in the interpretation and application of the criteria, along with a failure to conduct a robust and transparent process of community consultation, will undermine public trust in the conduct of emergency research. The primary source of ongoing controversy is the interpretation of the criteria

that available treatments are either "unproven or unsatisfactory."

The criterion "unproven" is fairly straightforward and should be interpreted simply as the absence of any proof of effectiveness. However, the criterion "unsatisfactory" is subject to a range of possible interpretations. This criterion should be stricter than the ethical requirement for equipoise that serves as the basis for controlled clinical trials. Rather, as suggested in the preamble to the 1995 proposed rule, the criterion "unsatisfactory" should mean that the available treatments failed to prevent a significant proportion of deaths, or mortality, or permanent disabilities, or morbidity. When there is a safe enough proven standard treatment, non-consenting research subjects should not have that treatment withheld in favor of an unproven intervention, no matter how promising it may be.

We are concerned that extending the exception from informed consent to include clinical trials between treatments that are in equipoise would, in effect, eliminate informed consent as a moral requirement for research whenever obtaining consent is not feasible, even if

available treatments are both safe and efficacious.

We support the clear distinction between community consultation and public disclosure that is found in the FDA draft guidance. However, we believe that the moral acceptability of research conducted under the emergency exception from informed consent rests on a robust process of community consultation and on the transparency of this process and of the conduct of the research.

Unfortunately, we believe that many forms of community consultation that are currently practiced do not satisfy the moral requirement for two-way communication. In particular, such a communication process must be open to the possibility that changes may need to be made in the protocol or other aspects of the research. We believe that the research protocol as well as informed consent documents should be available to all members of the community on a routine basis. It is a problem that this is not required. In addition, the requirement for an opt-out mechanism should not be used as an excuse to withhold such documents from members of the community who have expressed doubts about the research.

The moral requirement for transparency in the process of community consultation suggests that the adequacy of such consultation should be readily apparent to all members of the community, including regulatory authorities, such as FDA and OHRP.

There are two procedural issues that we do not see addressed either in the FDA draft guidance or in the questions posed in preparation for this public meeting. First, the regulations require that an IRB which cannot approve the research report this to the sponsor, who then must report this to FDA and to other involved IRBs. We believe that this requirement is consistent with the moral importance of transparency and community dialogue that serves as the foundation for this type of research. We are aware of instances when an IRB has raised questions about the appropriateness of certain research under this regulation, only to have the investigator, at the behest of a sponsor, withdraw the protocol from IRB consideration. Since the IRB had not taken a final action, the concerns of the IRB were not reported directly to the sponsor nor to FDA or other involved IRBs. We believe that any action by an

IRB, including a failure to take action based on concerns raised subsequent to the submission of the protocol, should be reported via the sponsor to the FDA and other involved IRBs.

Second, we are also aware of emergency research under an exception from informed consent taking place under a Special Protocol Assessment that has been granted by FDA.

It is our understanding that such an assessment means that there can be no changes in the protocol based on subsequent ethical concerns that are raised during the process of community consultation. We believe that granting a Special Protocol Assessment for emergency research to be conducted under an exception from informed consent is contrary to the spirit of transparency and to the two-way communication which FDA cites in its own draft guidance. Nor should the FDA be forced by its own regulations to allow research to move forward despite serious ethical shortcomings revealed during the process of community consultation and/or during IRB review.

Before concluding, as a pediatrician who has conducted research on the application of an exception from

informed consent to the obtaining of parental permission, I should add one comment about pediatric research. The feasibility of informed and voluntary parental permission remains an issue even if the parent is physically present at the child's bedside. Although parents want there to be a process of communication, our research supports the view that a narrow therapeutic window, such as 30 minutes, may not provide sufficient time for a parent to make an informed and voluntary choice to permit a child's enrollment in emergency research.

Nevertheless, there should still be a carefully thought out process by which the parent can opt out of having the child participate in such research.

Although the criteria for such research remain the same, the practical application of these criteria in the context of pediatric research needs to be evaluated on a case-by-case basis. In addition, there should be active involvement of parents drawn from the appropriate communities in the design and conduct of such research.

Finally, we support the view that research to be conducted under an exception from informed consent be

subject to an initial public discussion of the appropriateness of the proposed research under the existing regulations. Such a public discussion is even more essential when there are substantive differences of opinion about the interpretation and applicability of such criteria as "unsatisfactory" and "practicably." As has been discussed, depending upon the sponsor, that public discussion could occur before either before an FDA advisory committee or under the auspices of an NIH council. I might add that the only difference I might see between calling that an IRB or not is whether local IRBs could then defer under an FWA to the opinion of that body as more than just simply an advisory body, but hopefully, they would ask and answer the same questions that an IRB would ask and answer.

The questions that could be productively addressed in such a public discussion include whether the research meets the criteria for being conducted under an emergency exception from informed consent, the communities that should be involved in the consultation, the appropriate processes for conducting such consultation, mechanisms for opting out, and other issues. In effect, such a meeting could serve as

the first event in a robust and transparent process of community consultation. We do not hold the position that all such research would, over time, require such a review. However, the use of such a review process would establish a worthy tradition. Over time, the public interpretation and application of the regulations would allow for the identification of protocols that would not require such a process. It turns out the RAC actually follows that same kind of a triage process as well.

Although we believe that there can be greater clarity and guidance about the criteria for conducting research using an exception from informed consent and improvement in the process of community consultation and the overall transparency of research conducted under such an exception, we do not believe that either the guidance or the process can be specified with such precision to obviate the need for ongoing public discussion and review of protocols conducted with an exception from informed consent.

Now, that's the end of my prepared remarks. Let me just make one other comment in response to some of the discussion about community consultation. You could outline

broadly sort of two different approaches to where community consultation fits in this process. One is the protocol fits the regulation, so let's go out and do the community consultation. There I think it would be for a fairly straightforward purpose of assessing the community's response to that protocol. The second would be if you're unsure of the fit, where that community consultation actually becomes a process of the design and conduct of the research, where you take to the community that's involved the very question as to whether they think the research is worthwhile enough to be conducted under an exception. And my own view is that I would privilege the view of the community, who would then benefit from that research in addition to the patients and the parents of those pediatric patients who may benefit from that particular research.

And the method I think is key. I don't believe that community consultation is for the purpose of protecting the community. That's for us, in the design of the research, to take care of. It's as much to assess the community's view of the appropriateness of the conducting of the research within that community, and the approach that I

would offer is one that we used in the research that I'm mentioning. It was focus groups, where you can use purpose of sampling. You go out and draw them in. You don't just open the door and see who arrives. And then you actually carry that research through to thematic saturation using qualitative research techniques to where you're fairly certain that you've heard everything that can be heard.

One of the challenges, is your group representative of that population? But that's something then that those looking at that would be able to ascertain.

And, as an aside, this work I'm mentioning was published in *Pediatrics* in 2004, and it was a community consultation for in-patient cooling after cardiac arrest in pediatrics.

So, we defined it to where we could go to the in-patient population and parents that were in-patient to gather the community, which is an easier task than trauma and EMS systems, and it was conducted with the IRB having approved the protocol and then the second step of community consultation. We didn't then carry out the trial because it was clear that a single-center trial of that question really wouldn't be effective in answering it, and there are current

discussions about doing that as a multi-center trial. But that's as some background.

With that, I'll stop and entertain any questions. Thank you.

ROBERT TEMPLE: Thank you. I know we're not supposed to argue with you, but let me tell you, the presence of an SPA does not ban amendments to a protocol. A Special Protocol Assessment is what it is, it says what we think of it, but if you want to put in the protocol and amend it later, there's no rule against that.

But I have a question too. You discussed the standard of what exactly "unsatisfactory" means for the standard therapy, and that plainly is a problem. And a counter-proposal was that as long as you're in equipoise about the two, that's good enough, and you didn't think that was good enough. We have at least one study that I won't describe, in which an approved therapy would be compared with the therapy that, let's say for the moment, people think is likely to be better in certain critical ways and is not an unknown therapy. It's used in some populations already. So, in that circumstance, "unsatisfactory" really

translates to people think they could do better and have some reason to think so. Do you think that's not good enough under the circumstances or would that be part of your redefinition too? That's really not the same as "no good at all."

ROBERT NELSON: Right.

ROBERT TEMPLE: It's well short of that. It's an acceptable therapy, but people think they can improve on it in an emergency situation that really matters. How do you feel about something like that?

ROBERT NELSON: Before I answer that, let me respond to your non-argument. (Laughter) What I would advocate is including clear guidance about that because, at least in trying to decipher the SPA regulations, all we could find was language about scientific concerns, and not ethical concerns. In other words, the protocol could only be amended based on scientific issues. If that's incorrect, wonderful, but I think then that would be just one--

ROBERT TEMPLE: Protocols can just always be amended. There's not restriction. It's just advice.

ROBERT NELSON: Right.

ROBERT TEMPLE: It's not a requirement.

ROBERT NELSON: In response to your hypothetical, I think that's where I would privilege the robust community consultation, and, personally, I would put that question to the community and just ask whether that's a reasonable thing to do. As I was listening to this, it would--you know, you would consider, for example, very differently an active control equivalence trial, where in fact you have two very close interventions, I think that would be viewed very differently than, say, a three-arm trial, where you had a placebo in that as well, which would be even more deeply problematic if, in fact, you're doing that.

The incremental risk, I think, argument would argue that the risk of such an active control equivalence trial, again, depending on the data that you've got to support either intervention, would be probably small, and I do believe there's good evidence that you're better off in a research trial often, not all the time, than you are getting off-label clinical practice, but I might point out at least the very trial conducted under an emergency exception was the cross-linked hemoglobin, where in fact if you got the

intervention, you did worse, and that was stopped by the data monitoring committee.

So, we could kind of debate back and forth, but my own view personally would be to privilege a robust community consultation around that very question, rather than precluding that from going, if you will, into that process.

ROBERT TEMPLE: Okay. That also suggests that you're somewhat sympathetic to the idea that different studies have different levels of risk associated with them, and that might affect what you do or how much consultation you get. Is that true also?

ROBERT NELSON: Yes. I have seen the AHA document as one of their outside reviewers and like it. So.... Like it now. (Laughter)

JEFFREY SHUREN: Other questions?

DENISE ZAVAGNO: I had a question about opt-out. You mentioned it in two different terms, and one was just a parent might choose to opt out. So, my question actually goes to the more general use of this notion of an opt-out provision when, let's say, a sponsor is conducting a multi-center trial and the sponsor offers the ability for people

to, you know, have some kind of indication that they're opting out. How practical do you think that is? And, for instance, if there are lots of these kinds of studies happening throughout the United States, if different people, you know, different sponsors offer different mechanisms for opting out?

ROBERT NELSON: I think there's two things that you've put together. One would be the ability to identify yourself ahead of time as someone who would choose to opt out of a trial should you become eligible, such as bracelets, if you're going to be hit by a car crossing the street and you don't want to receive artificial blood substitute. That's a very different question than it is asking someone if they're even capable of being asked when they first arrive, "Do you or do you not--do you want to be in research or not?" My opt-out comments are related to the latter. In other words, everyone should have that question asked. I wouldn't consider that consent.

DIANE ZAVAGNO: Right.

ROBERT NELSON: What you're really looking for is this sort of visceral reaction on the part of some people

about "No, I don't want to be involved in research." And that's it, and how you ask that is going to vary from study to study, but it's a very short kind of question. And those that don't have that kind of visceral response to research would probably say okay. The broader opt-out mechanisms, I think, are more challenging, and I don't think I really have anything enlightening to say about it. So...

DIANE ZAVAGNO: I mean I think that is something we do want to hear from people on, is how practical that would be from, you know, the broader issue. How could it be done and be meaningful?

ROBERT NELSON: Well, really the only experience I would draw from are perhaps those that have DNR orders within EMS systems. There are mechanisms by which people who feel strongly about something can identify themselves as someone who doesn't want something, and the only clinical analogy I would know about would be trying to respect Do Not Resuscitate orders within EMS systems and state legislation that allows for that kind of prior identification, often using a document, sometimes using a bracelet and the like. That clearly depends upon your ability to get information

out to the public, which, we've already heard, documentation is problematic. But that could work.

JEFFREY SHUREN: Other questions? Thank you very much.

Next I'd like to call Dr. Joseph Ornato and Dr. Joseph Minei, National Institutes of Health, National Heart, Lung, and Blood Institute and the Resuscitation Outcomes Consortium.

JOSEPH ORNATO: Thank you very much. My name is Dr. Joe Ornato. I'm a cardiologist and emergency physician.

I'm professor and Chairman of Emergency Medicine at Virginia Commonwealth University Medical College of Virginia in Richmond, Virginia. I'm also the EMS Medical Director for the City of Richmond and the Fire Department, and I have the distinct honor of also serving as the Cardiac Co-Chair for the NIH-sponsored, NIH/NIHLBI-sponsored Resuscitation Outcomes Consortium, affectionately known by us as ROC.

My colleague, Dr. Joe Minei, is involved in the surgical side, and I'll have him give you his titles.

JOSEPH MINEI: I'm Joseph Minei. I'm the professor and Vice Chairman of the Department of Surgery at

UT Southwestern Medical Center in Dallas, and the Chief of Surgery at Parkland Hospital, which is a regional level 1 trauma center that serves the Dallas Metroplex. My role in the Resuscitation Outcomes Consortium is to serve on the Executive Committee as the trauma principal investigator.

JOSEPH ORNATO: Thank you. I will be giving the brief formal comments, and then we'd be delighted to try to address any questions from the panel.

Sudden, unexpected out-of-hospital cardiac arrest and major trauma, as everyone knows, claims hundreds of thousands of lives per year, and we've learned in the ROC consortium how they share many common physiologic mechanisms and challenges. From a public health standpoint, cardiac arrest and major trauma have no equals. The numbers of people dying from these conditions are absolutely staggering--equivalent to one or two jumbo 747s full of passengers crashing and killing everyone on board every single day of the year. Cardiac arrest and major trauma can strike virtually anyone, from cradle to grave, no warning, and in an instant they can turn a healthy productive person into a victim only minutes from biological death. Despite

what the American media depict on television, where almost 70 percent of cardiac arrest victims receiving CPR make it out of the hospital alive and well--and that was actually documented, as some of you may know, in the New England Journal about 10 years ago--the actual odds of surviving a sudden, unexpected out-of-hospital cardiac arrest in the United States are only about 5 percent--1 in 20, not 3 in 4.

In large cities like New York and Chicago, where traffic congestion and high-rise buildings make it difficult for emergency crews to reach victims quickly, reported survival from cardiac arrest averages only one in 100. Major trauma victims are not much better off. Approximately 175,000 injury-related deaths occur in North America each year, and life-threatening traumatic injury is the leading cause of death for persons 1 to 44 years of age.

The National Institutes of Health/National Heart, Lung, Blood Institute-sponsored Resuscitation Outcomes Consortium is approximately 2 years old now. It's, approximately, a 50-million-dollar governmentally sponsored clinical trials network with a mission of conducting adequately powered randomized clinical trials that can

determine whether promising drugs, devices, and therapeutic strategies can improve neurologically intact survival from out-of-hospital cardiac arrest and major traumatic injury. The consortium includes investigators, study coordinators, and public safety/emergency care providers from 11 different geographic areas representing 8 United States and 3 Canadian sites. Like our colleagues in the Neurological Emergencies Treatment Trials and Pediatric Emergency Care Applied Research Network, or PECARN, our clinical investigators and their teams have extensive experience with the exception to informed consent procedures, not just in our recently launched and developing ROC trials, but from roles that many of them and us have played as investigators, clinical trial leaders, emergency care directors, or public safety personnel in prior studies, such as the Public Access Defibrillation trial, the ASPIRE study, and the recently completed Polyheme study. We appreciate the opportunity to provide our input to the FDA's draft guidance relating to the exception to informed consent requirements for emergency research.

In general, the ROC investigators believe the

existing exception to informed consent procedures for emergency research strike an appropriate balance between the need to find more effective, safe treatments for imminently life-threatening, incapacitating conditions and the rights of individuals in our society. Our experience is that the criteria for allowing studies under 50.24 provides adequate protection of human subjects and permits conduct of scientifically rigorous research. The existing regulations and the draft guidance document are generally well written and of great value to investigators seeking to conduct such research with the highest moral and ethical standards, particularly in the areas of study design and execution, public disclosure, and community consultation.

The ROC investigators support the opinions and recommendations expressed by our colleagues in NETT and will not repeat or elaborate further on their points today. We believe that a central IRB or other experienced national panel could be considered as an option for advising local IRBs that either have little experience with the emergency exception process or are struggling with a particularly challenging issue. However, we do not support requiring all

proposals to be reviewed by a central IRB because we're concerned that it may delay implementation of important research studies without adding significant value to the process.

Since the majority of ROC study populations are adult, we will target our comments primarily to research on adults, knowing that many of the important, unique issues pertaining to emergency research in children are being addressed by our colleagues in the PECARN network. We'll focus our comments on two issues. We have provided for the committee answers to the questions posed in the consent notice in our electronic submission, and we will not go over those in detail.

So, our two issues are as follows: First, the need to stratify the intensity of community consultation and public disclosure based upon the anticipated incremental risks to subjects of participating in a research study.

A major purpose of the FDA draft document is to provide guidance to investigators, IRBs, sponsors, and others on implementation of community consultation and public disclosure. A number of the questions being asked of

this meeting's participants center on whether there should be a minimum level of community consultation or required public disclosure elements pre- or post-study. We support the position of our colleagues from the American Heart Association and agree that there should be minimum guidelines for each of these areas, but that the minimum level of community consultation and public disclosure should be based on the incremental risk associated with the study interventions. And I think that point was made beautifully by our colleagues from AHA earlier.

Our second point centers around the exception from consent for emergency research, and we believe that it should extend to review of the medical record to the time of hospital discharge as the standard in emergency research. 21 CFR 50.24(b) currently states that "IRBs must ensure there are procedures in place to provide information about the emergency research study, at the earliest feasible opportunity to the subject, if the subject's condition permits this; the subject's legally authorized representative, if the subject remains incapacitated; or the subject's family member, if no legally authorized

representative is available, including notice that participation in the study may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled."

The ROC investigators agree with these requirements, but suggest an important modification that would permit the exception from consent for emergency research to extend to review of the medical record to the time of hospital discharge as the standard in emergency research. Once the experimental intervention has occurred, the physical risk of inflicting harm, whether evident immediately or after some delay, from study participation is over. Currently, when a patient or other suitable representative as defined in 21 CFR 50.24(b) is informed that the patient was a subject in a research study under the emergency exception, they're given the option to withdraw or discontinue participation in the study. We agree that standard, written informed consent procedures must be followed for further interactions with the patient or their family, such as follow-up tests, interviews, or other evaluations. However, as discussed in a recent paper by

several of our ROC leaders and team members--and we've provided you the reference in our written submission--review of the clinical record is necessary to determine important outcomes, such as survival to discharge. If consent is required for this review but not granted, then these data are missing during analysis. Since seriously ill or disadvantaged patients may be less likely to assent, then investigators cannot determine reliably whether these vulnerable patients were harmed by the intervention. If missing data are different from complete data, then the analysis is susceptible to bias, and the conclusions could be misleading. Thus, without access to subject records for review, the investigators will be unable to ensure timely safety review, and study results are likely to be biased significantly.

We believe this is not just a theoretical concern, but is actually a common problem in clinical trials that involve patients at high risk of death or other adverse events. Many of us in ROC were involved in the Public Access Defibrillation trial. That trial required investigators to train over 19,000 volunteer lay rescuers

from 993 communities in 24 North American regions. There were more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of AEDs--30 survivors among 128 arrests--than there were in the units assigned to have volunteers trained only in CPR--15 survivors among 107. The P value was 0.03. Had only a couple of patients or families denied consent for the investigators to determine whether the patients survived to hospital discharge, this landmark positive trial would have appeared negative, since it's customary for an experimentally treated patient whose outcome is unknown to be assigned the worst outcome, i.e., death, the control patients the best outcome, i.e., survival. Another example is the DAVID trial, and I won't go into the details, but we've provided them in writing.

We believe the solution to this dilemma is to extend the exception from consent for emergency research rule to include review of the clinical record upon hospital discharge as the standard in emergency research. The only potential risk to patients associated with review of the clinical record after the intervention is loss of privacy

and confidentiality. We believe that appropriate safeguards already exist under HIPAA to minimize this risk.

Finally, our ROC leaders and investigators cannot emphasize enough how critical it is for clinical research to continue to make progress in treating life-threatening emergency conditions, such as cardiac arrest, trauma, and other acute, incapacitating disorders. The public health consequences of these medical and surgical emergencies are staggering, and we as a society have a moral and ethical obligation to find more effective and safe therapies. It is not possible to conduct live-saving research in the pre-hospital emergency setting without the provision for exception to informed consent. We applaud and appreciate the efforts of DHHS and the FDA in soliciting input on the draft guidance relating to the exception from informed consent requirements for emergency research. We believe that, with relatively minor modification, the regulations and draft guidance strike a reasonable balance between the need to conduct ethical, potentially life-saving research to find more effective treatments for critically ill and/or injured subjects and the need for human subject protections.

Thank you.

JEFFREY SHUREN: Thank you. Let me ask regarding this central IRB or advisory committee, you had said that this body could advise local IRBs, but it wouldn't be required. Let me ask, do you have thoughts in terms of would there be criteria for when someone would go to this particular body--for example, would this be tied to incremental risk? And, secondly, who would have the ability to call on this body? Is it FDA who would decide? Is it up to any particular IRB to go to this national body?

JOSEPH ORNATO: Thank you for the question. I have to share with you that there was a fair amount of discussion amongst ROC investigators and leadership on this very subject, and as one might expect, with a fairly wide range of individuals and a great deal of experience on the part of many of the individuals, there were some different opinions on exactly what our official position should be, because it is a complex question and it offers opportunities as well as challenges in terms of how you would actually execute it.

In the end, it was very clear that the consensus

was as I stated, that the group felt that such a body could be of value, and its particular value would be on perhaps some of the more thorny issues or issues in which a particular IRB might not feel it had a lot of experience with the exception to informed consent procedures. And in that regard, I think the sentiment was that it shouldn't be turned to, the central IRB shouldn't or the central body, whatever it's called, shouldn't necessarily just be turned to in high-risk, or not low-risk, procedures, but rather that it might be a resource that would be available for circumstances in which an IRB felt that it might be beneficial to get a more experienced body that, over time, would accumulate a great deal of experience with this process and weigh in on their opinions.

So, in the end, I think we felt that it would be helpful to have such a body, but that it's essentially the local IRB that should make a judgment as to whether it would be helpful to tap into that resource.

ROBERT TEMPLE: The question of data from people who've opted out of the study is obviously a thorny one. It also comes up in routine studies that don't involve

emergency research. Can you make any distinction between something like vital status, which is, in some sense, part of the public record anyway, and the other information, like the rest of the person's hospital record and--well, do you make any distinction?

JOSEPH MINEI: The point that you're making is obviously an important one, and when you take a look at a patient who decides to not give assent to continued care, the obvious important question is, what is the outcome? And I think part of the answer to your question is what are the outcomes that are specifically being looked at. Perhaps in a simple live-die, then maybe vital statistics could be looked at, but I think we're getting to a point where we're looking at different outcomes than just live-die, where the ability to look at the medical record is a necessity in order to determine safety of procedures that were performed in the pre-hospital setting. So, I think that it really is an important aspect, as we bring forward here, that we do have the opportunity to look at the medical record for these safety conditions as well as the outcomes as defined by the study.

JEFFREY SHUREN: Diane?

DIANE MALONEY: I had a question. I've heard, I think we've heard a couple of times today now recommendations to consider stratifying the intensity of community consultation based on the incremental risk. And from reading the comments and listening, I think I'm hearing that that goes to sort of the amount of community consultations and the back-and-forth, but do you think the level of information or the detail, you know, how much information you would provide in community consultation should vary depending on the incremental risk? And, again, recognizing that the audiences will vary and so you would tailor to the audience, but assuming a similar audience of, say, for instance, parents in a pediatric trial.

JOSEPH ORNATO: Well, I guess my response to that is I think there are certain fundamental elements that, no matter what the trial, clearly need to be conveyed, and I'm not sure off the top of my head I feel confident I can list all of them, but certainly the essential elements of the trial; a bit of a background on why it's being conducted; certainly some information about the condition itself; the

kind of subjects that are involved; briefly the design; any potential concerns about risk or safety involved in the trial; the kind of monitoring, supervision, oversight, and review that's taking place--I think, you know, many of the elements that really are providing transparency, so that someone attending a meeting or a focus group, hopefully, would feel that they've gotten a good briefing on really what's going.

As far as how intense it should be, I guess I think that probably should be factored in because a trial that does involve a certain amount of potential medical risk--and I'll give an example. I recently chaired a DSMB for a European trial that involved giving a thrombolytic drug to patients during cardiac arrest. That's a different domain than a trial that perhaps is looking at two different ventilation rates, something actually that we're looking at doing as a next trial in ROC, that are within standard practice, that are, you know, in need of, we believe, further clarification in terms of whether it's better to ventilate a little faster or a little slower, knowing that right now there's a pretty broad bell-shaped curve as we

look at what rescuers do.

So, I think, you know, the latter kind of a trial probably has very little risk associated with it, at least in our opinion, because it's essentially standard practice.

Right now we're just trying to fine-tune it. But the former trial, which is clearly not standard practice, which involves administration of a drug for an indication that is uncustomary to say the least, nonetheless, at least at the time, was a promising hypothesis turned out to be a negative trial. That kind of a trial, where the drug has potential known complications I think has a bit of a different requirement in terms of the review certainly and, I believe, the disclosure as well.

DIANE MALONEY: Can I just ask a follow-up question? I haven't heard a lot of discussion today about public perception-- I mean I know community consultation, but public perception. I think at least a number of people in the public who are not very informed about clinical trials, if they were to hear about a study after the fact, especially a trial in which somebody, you know, died, and heard that somebody was entered into a study without

consent, the reaction would be "Oh, my gosh, that was not the right thing." I mean some people would react that way.

So, recognizing again this notion of incremental risk, even if there is less risk, where do--do you see some benefit, though, in still having a lot of consultation early on because of the public perception?

JOSEPH ORNATO: Absolutely. I think that the risk to a study, the risk to investigators, the risk to all of us who are involved in trying to make progress on conditions such as major trauma, cardiac arrest, neurologic emergencies, and the like, the risk is from us not being as careful, cautious, and open as we possibly know how to be within reasonable, practical limits, because I think, you know, the American public, at least as those of us who work in this area have seen time and time again, have provided us repeatedly excellent input and feedback in the consultations that we did. The PAD trials is a good example. We got some, I think, really helpful ideas from our citizens who were involved in communities participating in PAD. And I think the concern that any of us have is to make sure that we really are in fact effectively communicating to the

public what it is we're contemplating doing, and under the guidelines that you've all provided, having an opportunity for them to talk to us and really provide us some feedback.

You know a lot of these trials are pretty straightforward, but some of them are highly controversial, like the Polyheme recent trial. And that's one of the reasons I think our group feels that there needs to be some flexibility, as I think you've written into the existing documents, to allow IRBs to really put the finger on the pulse of the local community and really figure out, you know, how much real rigor, maybe extra rigor, needs to be provided until everyone feels that they've really done their job properly in informing the community and really hearing back from them on how they're reacting to the, you know, the project that's being proposed.

JEFFREY SHUREN: Other questions?

JOSEPH MINEI: Can I add just one thing to that? I think if the--I agree, obviously, with what Dr. Ornato was saying, and I think the importance in some of these things is the background, and that is we may have what we consider a low-risk study in a high-risk population, and, for

instance, that may be getting a little out of my league here, but does the evaluation of two accepted drugs in cardiac arrest and looking at one drug versus the other, that would seem to be relatively low-risk in a high-risk population where we know that most people who have out-of-hospital cardiac arrest are going to die. So, I think it's very important that we have those initial discussions, even if we look at the incremental risk in the study as low, the population at risk might be so great that those are important points to make.

JEFFREY SHUREN: Thank you. Next I'd like to call Dr. Paul Pepe, U.S. Metropolitan Emergency Medical Services Medical Directors Consortium.

PAUL PEPE: Thank you very much, and good morning, everyone.

First of all, I want to say that I've really been very pleased with the rules that have been developed. There was a lot of hard work that went into this, despite a lot of times uninformed, I think, rhetoric or political pressures in different ways. In fact, this has been a good job. There's some fine-tuning that could be done. We've heard a

lot of it, and by the way, in terms of education, the three Rs of education, which is repetition, reiteration, and redundancy, you'll get some more of that today. So, I hope that I'll make some new points as well as I go through this.

You heard that I was representing the U.S. Metropolitan EMS System Medical Directors. These are--it's a consortium that's really not an organized group per se, except these are people who have a position, who are final decision-makers, in terms of protocols and medical care delivered to about 50 million Americans. They represent the medical directors from Secret Service, FBI, White House Medical Unit, and the 25 largest cities in the United States. So, they have major interest in this, and I'm, hopefully, reflecting the major sentiments coming from most of them as I do this today. And the group, as I said is, again, responsible for the resuscitative and other medical emergency care that goes in that pre-hospital setting, you know, before people get to the hospital, et cetera.

Now I basically want to give you, as a way of background, I've been involved in the area of doing this kind of research for many years and starting out in the

Seattle system. I've been, actually I've been a public servant now--my paychecks have come from either municipal or state governments--for the last three decades. So, I look at myself, first and foremost, as a public servant, and I try to be a public steward and a protector of the folks that we serve here. And actually I do have a conflict of interest, by the way, though, outside of that, my conflict of interest that I'm, being over the age of 35 and my wife is a woman 45 years of age, and therefore we are at risk for sudden death, okay? We care about this stuff. And also I drive --I also drive an automobile sometimes in the hours where there's people on the roads who have too much blood in their alcohol system. (Laughter) So, we are all at risk here, et cetera, and my children as well.

Okay. So, our story begins at, when we conducted a lot of trials early on, we actually used exception to informed consent. I've been involved with probably over a dozen studies between the city of Seattle and later in Houston, but the cool part was that the public thought this was great. They really wanted it and our cities to be part of what we were doing. We thought that was our mission.

And when they did a 60 Minutes on us back in 1978 saying, "If you're going to have heart attack, have it Seattle," it was largely based on the research that we were doing and that, you'll see in a second, I call "research" "re-search."

In other words, quality assurance of what we're doing to make sure we're doing the right things for the public at all times.

Later, when I got to Houston, I was even more sleepless because we conducted nearly a dozen clinical trials in that setting. And part of what I'm going to tell you is that a large part of this was that we're here about today talking about community consultation was just, was a de facto thing we were performing at that time. Up-front, prospectively, we were informing people in the public setting, through the media, et cetera, and elected officials what we were going to be doing, and I'll explain why, I think, as we go through this in just a few minutes.

So, I'm now in Dallas and part of the ROC, and I'm responsible largely for the community consultation that goes on for that particular thing in our area, et cetera, and I have a lot of data here to show that a lot of this was

prospective. We get front-page headlines whenever we put out a study that we're doing or whatever, and you'll see all the letters here from everybody from the mayors and the City Council members and the news directors of every station, how much they support these efforts. And part of that is the prospective involvement of people understanding what this is all about.

So, let me go through this. The cognitive roadmap for today will be to, basically, at the end of the session, I hope that you'll understand that the exception to consent concept is absolutely crucial for the people we serve, that many currently accepted treatment plans are empiric and may even be harmful, and that even FDA-approved interventions have not been confirmed as life-saving--I'll even point out that they may even be detrimental in some cases--and that millions of American families are denied the right to the most advanced care because sometimes you're getting the standard of care, et cetera, which we think is probably a problem; and then as a result, hundreds of thousands have really died needlessly, as I look back now, as a result of a lot of our inaction of not studying some of these things

earlier.

So, the community consultation concept is sound, but it does have some limitations, and we'll go through this in a few minutes. And if we're going to continue the way we're doing it right now, without stratification, funding is going to have to be provided, so we're going to have to pay for this because it takes time and effort to do a lot of the, the way this has been interpreted. And also I agree with what we've heard earlier before, was that there's a need to refocus on key targets and that there has to be a need to adopt a new perspective, as I've heard from the previous speakers. This is our public trust that we've got to be doing this stuff.

So, going out from here, I'm going sort of start off and say why I think that informed consent is so crucial to people. It's going to be, again, reiterative of what you're heard today, but to put it bluntly, trauma is basically the number 1 killer of those less than 45 years of age, but I think, more importantly, as you've heard from Dr. Biros, the kids have to be looked at. There, it's the number 1 killer of our children, and that's an area of great

concern to me and, I assume, everybody else in this room. The World Health Organization says this is something we should be worried about, because not only is it the number 1 cause of death worldwide, but for every death, four times as many people have permanent disability that may be been prevented if we had acted sooner with certain ways. And also they think, by the year 2020, it will exceed infectious diseases as the number 1 cause of loss of adjusted, productive years of life.

It's a big deal, and it's getting worse, and we need to be on top of this. And, as you heard earlier today from Dr. Dutton, that we basically also have the increased risk of terrorism, so therefore, it's a politically attractive thing to look at as well, even though I'm more worried about driving down the Central Expressway today than I am from getting killed from a terrorist. So.....

All right. Likewise, we heard about sudden cardiac death. I think I want to really point out the obvious here because it's like Dr. Ornato just said, I mean these are some of the most reversible things of the things we can do and we can save lives a lot more lives if we do

focus along these areas. With out current protocols, we state 5 percent. Actually I think that--Lance Becker and I came up with that number; we think it's actually a lot less than that. We actually qualified it as less than 5 percent, and yet it's totally reversible. For example, in the cases of ventricular fibrillation, the live-saving potential is amazing. Most of you have heard about one of the studies we conducted at the airport in Chicago, and in that area we actually found a first year of study that public deployment, which was controversial because we're letting people do this without any kind of informed consent, without, you know, the subjects being, who are going to be studied, like the public, you know, we're going to use this--it was a big deal. And yet, part of that study was to see--we knew that children could use these without any further instruction. So, we wanted to see how this would play out. And of the nine cases in that first year that went down right in the terminal area, right in the terminal and right in the gate areas, the ticket counters, 100 percent were saved that year. When I say "saved," most of them were waking up before traditional EMS even arrived. So, think about the

implications for the traditional way of approaching this, where people usually end up on ventilators, even the survivors, for several days. We know the potential is tremendous. And by the way, on that other issue about people, it turns out that six of the people in these cases who aptly operated this thing had never actually been trained in it or operated it. They had just heard about it and followed the instructions.

The point is, is that this is a highly reversible process, and we know it. It's kind of a "duh" statement, but I want to reinforce this, because if you're looking at less than 5 percent, there's a problem. But, you know, there's more to that. Nevertheless, AEDs are not available everywhere. I don't know if we have one in this building or not, but even if we do in the future, I'm may be on a boat or on a ski slope or something else, or you may not always have it available, and also many cardiac arrests are unwitnessed. We have to see if we can get people in other phases, metabolic phases, of arrest or whatever, ischemic phases of arrest. And many arrests are not "shockable."

Now, here's the interesting thing: Many life-

saving devices we think are life-saving are still unvalidated. They've been shown in preliminary trials to be very effective in experimental circumstances. And even those that are FDA's. And yet we haven't validated them. I'm going to show you in a few minutes why I think that's so important. A couple of things, for example, that are FDA-approved are things like the Impedance Threshold Device or the EZ-IO intraosseous infusion. The question is, is that if it costs my government, my city, my fire department \$70 a head to use these, am I absolutely sure we should spend them? Because that will be an impact of \$70,000 next year for us, just in the city of Dallas alone, for example. And we want to know the answer: Is it validated in multi-center studies? And yet this is FDA-approved. But to do that, and this is where the stratification issue comes in, I'm going to have to go through a whole period of community consultation, when it basically is something that may be a standard practice in some communities right nearby us, et cetera. Or can I just do a quality assurance study, as I look at this, and see if it really does work? And the big issue there is just the randomization issue, which we'll

come to. Because we, you sort of heard, jumping ahead, people said should we do community consultation for a, if we're just doing a ventilation rate? So, part of it may be, are you going to get this device? Someone saw I got it, but someone else didn't. And the way we do this particular study everybody's going to get a device, but some are going to be inactive. But still people want to know. The biggest problems I have in our communities have not been whether or not I was entered into a study and treated like a guinea pig. That's not what happens. People say, "How come I didn't get the device? How come half the people got it?" It's actually just the opposite in our communities, where we find that. And that's an important reason to educate the public, the officials, the media, ahead of time, of the importance of doing controlled trials, and I'll give an example here in a second.

The problems that even FDA-approved interventions have not been confirmed as life-saving is important because many currently accepted treatment plans, which have been empiric and, I think, logically make sense, have been actually found to be harmful, and I'll give you a couple of

examples. As a result, hundreds of thousands of Americans have lost their lives because we haven't studied these things or done the quality assurance, is what I call it, okay, as a routine. An example would be that widely accepted standards of care, such as fluid resuscitation for trauma, as studies that are done by Dr. Dutton and also myself have shown that in certain populations, they not only have no clear advantages, the current things that we use, but they actually may be detrimental, particularly in cases of uncontrolled hemorrhage. So, if we hadn't done those kinds of things, a lot of people may have lost their lives.

So, again, "research" to me sometimes sounds like people are doing, experimenting in a laboratory, when I think it's just basically fine-tuning what we are doing and looking at this.

More impressively is that when you conduct these trials on a regular basis, which, what we try to do is to try to make sure that we're constantly in that mode as much possible. We do it because it saves lives. And a classic example of that is the first thing I ever actually did in the city of Houston, which is the anti-shock garments.

These were required by law in two-thirds of the states, to be carried on the ambulances, and it made sense because they raised blood pressure, and that seemed like a good thing. As it turned out, probably raising blood pressure before you get control of internal hemorrhage may be a bad deal. So, as it turned out, we studied it, and we were entering it--it was required by law, but we said we'll do it on an every other day basis, because this was difficult to blind, of course, et cetera. So, as we did that, you have advertisements out there saying that controlled shock can save lives, yet when we did this, we had baseline survival of 50 percent for the group re-entering, those who had gunshot wounds to the chest and belly. As we ended up doing this, what we found was that the MAST group, after the first 6 months of study ended up getting nearly a 70 percent survival. That's a 70 percent improvement over baseline. So, if you did a historical control, you would have said, "Wow! Cat's pajamas! This is great stuff." But had a control group that had a 78 percent survival rate, okay?

But the thing is, you said, well, we introduced this horrible device. It was the standard of care. And the

interesting thing about this is that we saved lives just by doing the study, not only because we protected people from the future, but there was closer scrutiny of care given, reinforcement of standard procedures--we got everybody together and decided what's the best way to do this--and prospectively, we improved survival for both control and study groups. And I think what's important is that we saved more lives. The advantage of being entered into the study far exceeded the detriment that was given by the thing that was standard of care, et cetera. So, tens of thousands of lives I think could be saved really from, on an annual basis, from doing this, and I think that's a matter of public trust.

So, anyways, I would say the other thing you have to point out, I really, you know, someone mentioned that it sounded kind of paternalistic, you know, when we heard previously from Dr. Dutton that the public basically doesn't really care. I think they do care, but they do have trust in us, and it's a matter of trust that they actually hope that we are doing this, we're giving them the best level of care, that we're constantly seeking for that. And they're

not aware of the day-to-day protocols. They really believe that--if you ask the average person that you go out and ask, what are we doing in the back of the unit, they don't have a clue. They trust that we're doing the best job possible, and we are trying to do the best job possible. And so, that's been part of the problem, is that, as we heard before from Dr.--I thought it was so articulately, it just really articulately, it very articulate the way that Dr. Maio said that there are uncontrolled experiments going on every day from well-intentioned people, and this is so much more straightforward because we know what the plan is. There is a concept of implied consent every day that meets the public expectations as a whole, but when you do scientific protocols, everybody knows the plan up front, et cetera, and it's a standardized approach that's known ahead of time, and I think that that's what's key.

Third thing is that public awareness is still important because what happens is the only people who I have found in my experience that complain are basically disenfranchised people, someone who's mad at the paramedics or mad at a City Council member or mad at somebody

somewhere, and basically come out and (indiscernible) or people who have not been well-informed or people feel like they're getting cheated. Here's the interesting thing. For example, in our community is the African American community, for example, I've met with a lot of them. Different times it would be pastors, et cetera. Part of it is feeling like they're often denied actually getting the advantages of care. And yet, what happens in the pre-hospital setting, where everybody gets the same treatment, there is actually an advantage that's given to under-served populations, et cetera.

So, community consultation is important, and I think that it's sound, but there's current rules-- limitations and rules, as you heard before, where you have to do it. It becomes obtrusive when you have cases of things where you're just basically looking at ventilation rates or whatever it may be or something that's already a standard of care that we're doing.

There needs to be a re-focus on certain targets. I agree--what I heard is that having focus groups out there, a lot community efforts--what we've done is we've done

studies with our media and our city officials, and we find that's not a useful way of spending your time getting the word out to the public. There are better ways of doing that. But you may have certain exceptions to that, for example, if you want to look at like particular patients that have heart attacks and get some input ahead of time for them, just, say, how should we conduct this or do you have any suggestions for us? I think that's fine.

There is a need for prospective relationships-- I'll be wrapped up in about 2 minutes, if that's okay. There is a need for prospective relations with the media, politicians, and health officials and all of those folks ahead of time, and also inspirational empowerment of the medics. And I think that, as Oscar Wilde once said, it basically is personalities, not principles, that move the age or that makes a difference. I have something that you can look through, the rest of the handout. I have some suggestions about the individual questions that came up.

But, in summary, what I wanted to say is that I think that what we heard today about stratification and I think there is an immediate (indiscernible) community

consultation and certain suggestions, although I still think that public announcement of certain things should take, if there is a randomization procedure, and that you basically have to start focusing more on mass media, focus on elected officials. Just think ahead: Who are people going to complain to? Make sure they are informed, they know what's going on, and it becomes less political under those circumstances, which a lot of this is about.

So, with that, I'd like to thank you very much. Thanks for indulging me in my sort of emotional rant here, but I hope that--I'm passionate about this because I really feel like we've lost thousands of lives by inaction, so.... Thank you.

JEFFREY SHUREN: Thank you.

SARA GOLDKIND: I would like to ask you if you could elaborate further on how you build this public trust that you've referred to--

PAUL PEPE: Absolutely.

SARA GOLDKIND: --and communicate this notion of public stewardship that you also mentioned. You said that there ought to be a stratification mechanism or assessment

prior to community involvement, that there ought to be some basis in that regard, in terms of a risk stratification, but that you--if I understand you correctly--you also said that you think that that kind of prospective community involvement is crucial. And I wanted to see if you could elaborate on how you communicate and create that trust.

PAUL PEPE: Yeah.

SARA GOLDKIND: And whether you see that as part of community consultation and/or public disclosure.

PAUL PEPE: Yes. Part of it is that we make ourselves part of the city government where we are. For example, I have--I'm basically a director in the city government and work for the mayor and the city and city managers. I work closely with the City Council members. I basically show that our survival rates are low because there's not enough bystander CPR, so we make sure that's communicated. We get them as part of the program. Not everybody's going to get bystander CPR because they're unwitnessed, so we said, what's the next step? What can we do to investigate that? And you make sure that they are aware ahead of time that the three questions that'll be

asked are, one, are we being experimented with? So, to be able to reassure people about the risk/benefit here. And the acid test for me, as I tell them, is would I enter my child into this study? Two is that they'll be asked about randomization and why that's important. I give you a classic example of why we have to do controlled studies and not historical controls. And three is just to be aware that this is a cool thing, that when you do this, you improve outcomes for all groups because we're studying things much more closely.

So, I began that process as soon as I arrived in the city in 2000, for example, and I did it back in Seattle.

We did it in Houston early on. And you develop relationships. It's human relationships, and people think it's a good thing. So, you start that before you even begin the studies, for even years.

So, what I'm going to show you here are letters that shows the education of everyone from news media to mayors to health commissioners, et cetera, and medical societies ahead of time.

Stratification issue. Okay. Some people in my

community will us dopamine for an overdose, for blood pressure. Some people use norepinephrine. And those are just two acceptable things in the community, so why don't I just study them head-to-head if I want to do a trial to see if one's more expansive or whatever, to see, does that (indiscernible) part of the community. And I don't think that in that situation we really need to do a widespread community consultation. However, if I'm going to do something that is FDA-approved, but we may not use it in half the cases, you know, for example, let's say something like the auto-pulse. It's FDA-approved, people are using it, but we're not sure that it's working, but you want to make sure, with half the people getting it and half aren't, you want to make sure they're informed, particularly at least the elected officials and the advocates. If you get on to doing things as Joe was talking about, like giving TPA, et cetera, now you're getting into a whole other realm where you do want to do lots of public thing and actually talk to people ahead of time and get feedback, all right?

JEFFREY SHUREN: Yes, Bob.

ROBERT TEMPLE: The, I'm familiar with the

infusion study referred to by Dr. Dutton. It's one of my favorite studies proving that you never really know what you think you know till you look. Is the pants study, is the trousers study published?

PAUL PEPE: Is it what?

ROBERT TEMPLE: Is the trousers study published?

PAUL PEPE: It was well-published back in the 1980s. That's one of the first things I started with when I got to Houston--

ROBERT TEMPLE: Under your name?

PAUL PEPE: Yeah. I can get you all those references. Those are straightforward stuff, I think. How many people are using anti-shock garments now? At parties maybe, or something like that, you know. (Laughter) Okay, good. Okay. But you know what? It's interesting because, when we weren't doing this, we heard from people that we were basically denying people this live-saving device, and that was the rhetoric that goes out. We have to change that mentality. By the same token, within 2 years, they were suing people in New York City, for paramedics, for using them after we had done our study, which is just, you know,

shows you a lot.

ROBERT TEMPLE: I mean who not give saline to someone who had been stabbed, really?

PAUL PEPE: Say that again?

ROBERT TEMPLE: Who wouldn't give normal, who wouldn't give an infusion to people who had been stabbed? It'd be crazy.

PAUL PEPE: I think most of us would give infusions even, even people like myself and Dr. Dutton, but it would be within limitation. It has to do with when we give it and often the timing of when we give it.

ROBERT TEMPLE: Right.

PAUL PEPE: I think then you get more nods in the heads in the room there. Okay? But saline--how about hypertonic saline? Let's study that. That sounds like a good one. (Laughter) Okay.

JOANNE LESS: One of the slides that you didn't get to said that the current IRB interpretation of the rules on community consultation may lead to unachievable and unnecessary disclosure.

PAUL PEPE: Yes.

JOANNE LESS: Could you explain that a little bit?

PAUL PEPE: I kind of did for you, but I'll give you, I'll just reiterate it, is that the issue is interpretation. Our IRBs often live in fear of having all their federal funding taken away if we don't follow the rules. So, they're almost, they're just almost like going nuts about some stuff. So, if I wanted to do that dopamine versus norepinephrine study, they're saying, "You better go out and talk to all the drug addicts in the city," you know, that kind of thing, "and make sure that they've been informed about this," when it actually could affect anybody or anybody's child, in an overdose of a young teenager, et cetera, but that's the example there, where I don't think we even need to go that far under those circumstances. I hope that explains it.

JOANNE LESS: Yeah. Thank you.

PAUL PEPE: Thank you. Thank you for asking and clarifying that.

JEFFREY SHUREN: Any other questions? Thank you very much.

PAUL PEPE: Thank you very much for the

opportunity to be here. Thank you. And I'll drop off the stuff with you here.

JEFFREY SHUREN: It is now 12:10. What I propose, we were going to go till 12:15, so we will again break 5 minutes early. We will pick up again at 1:45, so that will give everyone just a little over an hour and a half. I understand the café upstairs has a few sandwiches.

(Laughter) If you want to make a mad dash--I see people in the back are already racing out. Otherwise, there is a list of restaurants in the area. But there should be sufficient time to go get lunch and come back. We'll see you in a little while.

(Break)

JEFFREY SHUREN: Why don't we go ahead and just get started? Just to let you know, we have (segment unrecorded) to speak. So, since we have the time, just in the interest of fairness, I'll give each of those individuals 15 minutes like other speakers in which to speak. It'll be the same rules of the road. This is the same rules of the road for the folks who have signed up to speak: 15 minutes.

With that, let me call Dr. Jeffrey Saver, American Heart Association--American Stroke Association.

JEFFREY SAVER: Thank you, Dr. Shuren, members of the panel.

I'm speaking today on behalf of the American Heart Association, its division the American Stroke Association, and over 22 and a half million AHA-ASA volunteers and supporters. The mission of the American Stroke Association is to reduce disability and death from stroke through research, education, community programs, and advocacy. We greatly appreciate this opportunity to comment on the draft guidance regarding conduct of emergency clinical research.

My experience in acute stroke clinical trials may be helpful to the panel's deliberations. I've been a participant in and leader of over 30 acute stroke treatment clinical trials supported by the National Institutes of Health and by industry, including the MERCI and FAST-MAG stroke trials that employed or plan to employ waiver of explicit consent in emergency circumstances. I am currently a professor of neurology at UCLA, where I direct the Stroke Center.

Let me begin by noting that the American Stroke Association would like to express its concern that, as far as we are aware, exemptions from explicit consent regulations have never been employed in any trial of drug treatment for acute ischemic stroke conducted over the past 10 years. We believe it is not a coincidence that this past decade is also notable for the absence of approval of any new drug treatments for acute ischemic stroke.

Acute stroke trials during these years have enrolled only a fraction of the number of patients enrolled in acute myocardial infarction trials and very few patients in the first 3 hours after onset, when treatments are most likely to be beneficial. Strokes often render patients unable to provide explicit informed consent, making recruitment of patients affected by an acute stroke difficult. Substantial progress in acute stroke therapy will occur only if waiver of explicit informed consent regulations are able to be more widely implemented.

I will address today six specific aspects of the draft guidance document that are relevant to stroke patients. First, the American Stroke Association strong

supports the draft guidance document's endorsement of morbidity endpoints in addition to mortality endpoints as appropriate outcome measures for select exception from explicit informed consent trials. Stroke frequently produces non-fatal, but disabling outcomes that deprive individuals of their cognitive and physical capacities. The fact that a majority of Americans rate major stroke as an outcome that is equivalent to or worse than death indicates the importance of permitting morbidity endpoints in exception from explicit informed consent trials.

Secondly, the guidance document mentions stroke patients who are comatose as an example of patients who cannot give consent. In both acute ischemic stroke and intracerebral hemorrhage, aphasia, an inability to communicate with language, is a far more common cause of non-competency than coma. We ask that aphasia be added to the example in the document, expanding the relevant phrases from "comatose patients" to "comatose patients and aphasic patients with impaired comprehension."

Thirdly, use of waiver of explicit consent mechanisms in stroke trials has been hampered by uncertainty

among IRB panels regarding what factors can be considered when determining if a trial is impractical to complete using explicit informed consent procedures.

The American Stroke Association strongly supports the guidance document's recognition as a salient consideration the fact that mildly affected patients who disproportionately can provide explicit consent may have much higher full recovery rates than severely affected individuals. This situation is common in stroke. Mildly affected patients almost always are able to provide consent, but often are uninformative when enrolled in clinical trials because they have a high frequency of good outcomes, even when assigned to control therapy. Moderately and severely affected patients often cannot provide informed consent, yet they constitute informative patients needed for clinical trials, as they have the capacity to show a benefit from the experimental therapy.

Fourthly, we request the guidance document clarify an additional aspect of the process of determining whether or not a study is impractical to complete using explicit consent procedures alone, namely, how long a delay in trial

completion for conditions like stroke is sufficiently undue that the trial is impractical? We urge FDA to make clear that for conditions like stroke that affect a large number of individuals, produce substantial morbidity and mortality, and have few currently available treatments, a delay of 6 months or more in the development of a new therapy should be considered undue and justify implementation of exception from informed consent.

Stroke exerts a tremendous toll on the American populace. The only acutely proven therapy, the clot-busting drug TPA, is given to only 1 to 4 percent of patients and cures completely only 1 in 8 of these, with the result that 99.5 percent of acute stroke patients do not currently receive a curative therapy. New effective therapies are desperately needed. Each year, about 700,000 Americans experience a stroke, and stroke is a contributing cause to 273,000 U.S. deaths a year. When more than 1900 Americans each day suffer a stroke and 745 Americans each day die from stroke, a strong case can be advanced that even 1 day's delay in developing a therapy for stroke is "undue."

It is against this tremendous daily burden of

disability and death from stroke that the moral imperative to protect subjects with diminished autonomy must be balanced. The American Stroke Association believes that a 6-month delay threshold is an appropriate demarcation for excessive delay in developing acute stroke therapies. When failure to use waiver of consent will prolong evaluation of a promising stroke therapy by more than 6 months, waiver of explicit consent should be permitted.

Fifthly, the American Stroke Association also requests more explicit language in the guidance document recognizing that a variety of non-Phase 3 trial types offer participants a prospect of direct benefit and would qualify for exception from explicit informed consent. We ask that the document state that pre-hospital feasibility trials of drug and devices, Phase 2 signal of potential efficacy drug trials, and 5-10K pathway technical endpoint device trials can, in individual cases, be judged to offer a prospect of direct benefit, in addition to conventional Phase 3 trials.

While definitive demonstration of benefit is not the primary overall aim of such trials, many are designed so that patients assigned to active treatment receive an

intervention hypothesized to confer a direct benefit. A late Phase 2 trial may be testing the two or three most promising dose regimens, each of which delivers drug at levels expected to be within a therapeutic range. Patients in all active therapy arms of such a trial have a prospect of direct benefit. Indeed, since such trials often randomize more patients to active therapy than to placebo as opposed to the 1 to 1 randomization typical of Phase 3 trials, such late Phase 2 trials offer in some ways a greater prospect of direct benefit for the patient than phase 3 trials. Similarly, a technical endpoint device trial that evaluates a device modification intended to accomplish a technical endpoint, such as recanalization, more effectively than a predicate device already known from randomized trials to improve clinical outcomes offers as great a prospect of direct benefit as a Phase 3 randomized controlled trial.

Lastly, the American Stroke Association supports the FDA's recommendation that the effect of delaying administration of a test article be taken into account when determining the portion of the therapeutic window to be

devoted to seeking informed consent from a legally authorized representative or the opportunity to object from a family member. For most conditions in which effective therapy is time-limited, including ischemic stroke, earlier treatment is much more efficacious than later treatment within the treatment time window. Some IRBs have considered requiring that trials wait until the very last minute of a theoretical time limit for therapy before enrolling patients under waiver of consent regulations. This approach greatly increases the likelihood of study failure, as patients are disproportionately enrolled only when a little salvageable tissue remains.

In conclusion, let me emphasize three key suggestions. We ask the FDA to clarify that, for a common devastating and poorly treatable condition like stroke, a delay of 6 months or more in trial completion is undue and should be sufficient to permit use of waiver of consent enrollment procedures. To make clear that select technical efficacy device and late phase 2 drug trials should be recognized as offering patient participants the prospect of direct benefit and to maintain the current guidance

documents' recognition that avoiding disproportionate enrollment of mild patients unlikely to demonstrate a beneficial effective treatment is an appropriate reason for approval of exception from explicit consent procedures.

Thank you for allowing the American Heart Association and American Stroke Association to discuss the draft guidance in this public meeting.

JEFFREY SHUREN: Thank you. Are there questions from the panel?

ROBERT TEMPLE: I guess a trial could enroll all comers, and would it be feasible, do you think, to consent the ones who can consent and not consent the ones who didn't? Would that be such a difficult thing to do that nobody could do it or--

JEFFREY SAVER: That is just what we're in the NIH FAST-MAG trial. We have had mixed feedback from branches of FDA, different stroke trial lists, about whether it's possible to have both an explicit consent and a waiver of consent mechanism in the same trial, but that is what we proposed for the NIH FAST-MAG trial, and we understand that there's a good chance it will, that--the explicit consent

was approved several years ago, and we understand the waiver of consent may shortly be approved.

JEFFREY SHUREN: I want to ask you, you had suggested that for treatments for acute stroke and similar conditions, that a delay of 6 months or more should be considered an undue delay. And, just curious, the basis for picking 6 months?

JEFFREY SAVER: Well, we originally had discussions with FDA and were told that they were thinking that 2 years would be an acceptable delay for stroke, and we therefore went to the organizations involved in stroke here, the American Stroke Association, the National Stroke Association, and the American Academy of Neurology, and had discussions in each of those organizations about what would be an appropriate delay. All of them considered 1 year or 2 years far too long a delay when there are 1700 patients affected each day by this condition, and each of them suggested delays of 6 months or less. And the American Stroke Association, the Stroke Council and its executive committee, concluded that an appropriate demarcation was 6 months.

JEFFREY SHUREN: To the extent--I won't put you on the spot now, but to the extent any analysis has been done or maybe you'd think to do in terms of supporting the 6 months would be helpful to us because having that information in the administrative record will be useful in our trying to pick a particular time cut-off. So, looking at what that impact may be on patient populations given the number of people who are affected, that might be useful.

JEFFREY SAVER: Be glad to provide that.

JEFFREY SHUREN: Okay. Any other questions?

All right. Thank you very much.

JEFFREY SAVER: Thank you.

JEFFREY SHUREN: Next I'd like to call Dr. Terri Schmidt, Department of Emergency Medicine, Oregon Health and Science University.

TERRI SCHMIDT: Good afternoon. I didn't know at the beginning of the day that I would wonder about being the letter "S" and having to talk to people right after lunch, but we'll do the best we can. I'm going to try hard not to repeat some of the things that are in my written comments that other people have already said, but a certain amount of

redundancy towards the end of the day I think is inevitable.

First of all, I want to thank you for this important meeting and working to develop draft guidance. This meeting and discussion are important because the need to perform resuscitation research poses a true ethical dilemma. I will comment from the point of view of both a researcher as part of the PAD trial and the ROC trials and also as an ethicist who has done a number of studies specifically looking at implementation of rules. And I'm going to skip my comments about why the science is important because I think that's been well documented, and try to talk more about what we know about the rules and how they've been implemented.

A number of speakers today have talked about the idea of a national IRB, and there's certainly a great deal of merit to that, but I do want to comment that we recently did a study of the IRB Chairs at medical schools around the country and asked them the question, would they support a national IRB? And only 6 percent of them did. So, at least in a questionnaire format asking the IRBs, they have concerns about a national IRB.

Little is known about the public perception of these rules. However, surveys of public willingness to be involved in research without consent have shown a willingness, but that it is dependent on incremental risk, and this supports the notion that incremental risk is not only a concept that researchers and IRBs have talked about, but that public actually think that incremental risk is important. No studies to date have actually evaluated the experience of patients who have been enrolled in these actual studies. There are a few studies, particularly the one done by Lynne Richardson with the VOICES study that looked at the community consultation in the PAD trial and people who were in the buildings where the study took place, but no actual studies of subjects who have been enrolled in these studies. And we think that that's an important area for further research, to actually get the views and opinions of people who have been involved in the studies.

So, with that introduction, I want to specifically comment on several of the questions that you all have asked.

First, are the criteria for allowing studies conducted under 50.24 adequate to protect human subjects and to

promote scientifically rigorous research? When asked this question, 70 percent of the Chairs of IRBs around the country stated that the criteria do provide sufficient protection. Of course, this means that approximately 30 percent of them at least had some doubt about them.

Also, as Dr. Biros noted, the Academic Emergency Medicine Consensus Conference on Ethical Conduct of Resuscitation Research was convened in New York in May of 2005. The objectives of this conference were to provide an overview of the current status of the regulations in order to increase understanding of how the rules are currently used and to explore areas of consensus on issues important to subjects, researchers, and regulators surrounding these regulations. Approximately 80 individuals representing 49 organizations participated in the conference, and one break-out group specifically addressed the question of whether the criteria protected subjects, and they advanced the following recommendations.

First, there are no outcome measures that define "protection"; therefore, it is not currently known whether or not subjects are protected under the current rules.

Second, care must be taken to protect not only the individual from harm during research, but also to protect society from unregulated research and the inability to advance science.

Third, some surrogate markers or methods of protection whose efficacies are debatable include data safety monitoring boards, the community consultation and public notification process, and institutional review boards.

Fourth, minimal-risk studies should be held to different standards of protection than those that involve more significant risk to the subject.

Fifth, a handful of studies have been published regarding community consultation and notification, but the majority are case studies. Those that are specifically designed to discover the most successful methods are hindered by a lack of formal outcome measures and tend to have negative results.

Follow-up data from community consultation and public notification process should be disclosed to the Food and Drug Administration and incorporated into study designs.

Seventh, focus groups and random-digit dialing have been suggested as promising methods of fulfilling the community consultation and notification process.

Eight, studies that need to be funded and performed that formally investigate the best means of community consultation and notification.

Nine, more funding for this research should be a priority in the emergency medicine and critical care communities. More data regarding terminated studies should be made available to the research community.

Ten, quantifiable markers of success must be validated so that research may determine the most successful means of community consultation and notification.

And, finally, data regarding subjects' and family members' experiences with exception from informed consent studies need to be obtained.

Other areas of consensus from the meeting can be found in its proceedings. Attendees demonstrated consensus regarding the need to further refine the rule. However, they agreed that current regulations provide adequate and appropriate protection to safeguard patients. There was

general agreement that current efforts to safeguard human subjects are effective, but participants agreed that refinements to and standardization of the rule would facilitate resuscitation research and enhance patient safety.

And then commenting on two other questions: What are the costs, benefits, feasibility of community consultation as currently required? And what type of venue would be best for this additional review and public discussion?

As noted, published reports on the Public Access to Defibrillation trial found that the study was reviewed by a total of 101 IRBs and median interval from submission to approval was 108 days. Another study found that the disclosure process required in excess of 80 hours of investigator time. And another found that the process leading to waiver added \$5,600 to a study that would terminate after four patients were enrolled in the study.

Current efforts at our institution and around the country have demonstrated that initiation of interventional studies as part of the ROC are delayed by 4 to 7 months by

the process of community consultation. Sorry. I've misplaced my page. And at the trial--goodness. It is after lunch, isn't it? [Laughter] My sincerest apologies. I've lost track of where I was.

In the ROC trial, we found that multiple means of community consultation including random access dialing phone survey, pre-existing public meetings, specific meetings convened on this topic, and a Web site. We are in the process of evaluating all of these means. In the last couple of days, I just got data from our community consultation process, and we did four different types of community consultation--the public meetings, the random-access dialing, going to specific community groups, and a Web site--and, interestingly, got quite different answers to the degree of concern about the studies. All of them were within the range of 80 percent or so positive, but there's enough difference that each of these means seems to give slightly different results in terms of community consultation.

We were, however, struck by the ineffectiveness of community meetings convened specifically on the topic of

research. Our participation rate has been very low despite multiple media attempts to encourage attendance, and this is consistent with what the public tells us. Our survey of emergency department patients and visitors found that few would interested in attending public meetings. Most lay persons prefer mass media and other means of notification and feedback when perceived as relevant.

Based on our preliminary experiences, we believe that the convening of meetings to discuss a proposed study is not feasible and is a waste of resources. Community consultation can be done via a combination of other methods.

Random-digit dialing allows a general overview of a random sample of the public, albeit it does not include the people who are homeless, who don't answer their phones, specific groups that aren't addressed. This can and should be supplemented by presentation and discussion at already scheduled forums and public meetings targeting communities or citizen groups that may be most likely to be enrolled or might have particular concerns about a study. Thus, for example, one might target citizen groups with specific concerns about blood products when proposing a study that

would use such a product. An open Web site also can be used to elicit opinion and comment.

Both the investigators at OHSU and the IRBs in this community find questions about adequacy of community consultation a vexing one. While supporting the concept, questions remain about how much consultation is enough and the best response to negative comments. Certainly the goals should include reaching out to members of the community most likely to be impacted by the study in question and approaching diverse communities. In any consultative process, one expects a vocal minority to be opposed to any study despite efforts to address community concerns. Questions remain about when that opposition raises to the level that should halt a study, when it should lead to modifications, and when it is time to move forward with the study. IRBs and researchers would appreciate guidance in this area.

So, in summary, the FDA rule surrounding exception to consent in emergency research needs to strike a balance between protecting subjects and allowing important research to move forward. The rule has been in place since 1996, and

there is now a body of experience with the rule and limited empirical research on attitudes and experiences with the rule. This experience shows that community consultation may be a valuable method, but its implementation has been difficult. IRBs continue to have questions about rule application and interpretation. In general, the lay public has not shown an interest in attending public meetings, and researchers express frustration about how to conduct the process in a timely and cost-effective manner, while protecting subjects. Novel approaches to community consultation should be encouraged and guidelines that establish criteria for acceptance of the community consultation should be established. Thank you.

JEFFREY SHUREN: Thank you. Two questions. First, from the break-out sessions from the meeting, you had walked through a number of recommendations that came out, one of them was actually a comment that "some surrogate markers/methods of protection whose efficacies are debatable include"--and this was the first time we'd heard it today. The data safety monitoring board activity. Could you maybe flesh out a little bit more what were the concerns that were

expressed?

TERRI SCHMIDT: You know, I don't have the details in front of me. I think the whole issue in that comment was that all of the things that are in the rule, although seeming to be good ideas, we don't have data to prove their value. And I think it was no more than that, and I think that the data safety monitoring boards were just added in their general consensus of we need to look at how effective each of those things are.

JEFFREY SHUREN: The second thing I wanted to ask, you had raised, you know, we need to maybe look at some novel ways to do community consultation. One of the things you'd put on the table is random-digit dialing, and I know issues that have been raised today are trying to target those individuals who might find themselves as subjects in an emergency trial in the future, and randomly going to the public. Do you see that as really a way of finding those individuals or are we more likely to just get a broad array of folks who it wouldn't affect in the first place?

TERRI SCHMIDT: We think that it depends again on the study, that certain studies, such as the hypotonic

saline study that is about to happen with the ROC, targets everybody, and so random-digit dialing is a way of getting the general community feeling. So, if your trial is very broad and anybody could be involved, that everybody in the community ought to at least have an opportunity to have an input, as opposed to a more targeted study. If you're studying asthma, just as a random example, you might want to target more people who have asthma, but for some studies, the whole community is involved. And that we don't think it's a method alone, but it does have the advantage of coming as close as at least I can think of as a way of getting a random sample. The one thing we have certainly found in the small number of people who attend community meetings, they are polarized on one side of the topic or the other. They come to the meeting with a pre-set "I'm concerned about it" or "I'm really excited about it." In PAD, for example, we had a lot of people who came to say, "Gosh, you know, I had a cardiac arrest and the device saved my life. Please go out there and use it."

JEFFREY SHUREN: And then, just lastly on follow-up, any data that you may be aware of or have regarding the

effectiveness of the random-digit dialing or the open Web site as a tool?

TERRI SCHMIDT: The data that I have is very preliminary because it's this study that we have just completed, where we're comparing the responses to the random-digit dialing, using the same survey tool for the random-digit dialing along with giving that survey tool at public meetings, giving that survey tool on the Web site, and asking the exact same questions three times. I can barely tell you the answer because I literally got the data from my researcher yesterday, and what we briefly have found is a fair bit of consistency in the response, but not identical responses, and I need to kind of sort out what the differences are.

JEFFREY SHUREN: If there's any way to get us information from that by the 27th of November, when the docket closes, it would be much appreciated.

TERRI SCHMIDT: I believe by the 27th I can have it.

JEFFREY SHUREN: Okay. Thank you. Other questions?

JOANNE LESS: Given the data from the PAD trial, that it took more than 3 months for the IRBs to approve the trials, I was curious if you have any insight as to why only 6 percent of the IRB Chairs didn't recommend a national IRB.

It sounds like all those local IRBs were grappling with some difficult issues, so I would think that they would have voted a different way. I was wondering if you had any insight on that.

TERRI SCHMIDT: I have limited insight. We did two steps in this process. We did a ten-person qualitative interview where we had some more in-depth answers and then this larger survey of all the IRBs. And, in general, IRBs' concern was about local control and local control of the community consultation process with the concept that only they know their local communities. Certainly, I think that they might be more intrigued by the process if a national group took on the science segment of it and the oversight, and then local communities still had control of their community consultation process. That is what we heard at least from the small group that we talked to.

JEFFREY SHUREN: Other

questions? Thank you very much. Next I'd like to call Robert Silbergleit, Neurological Emergencies Treatment Trials.

ROBERT SILBERGLEIT: Thank you for allowing me to speak here today. I'm representing the Neurological Emergencies Treatment Trials, or NETT. It's a multi-disciplinary group of investigators that's been organized to perform clinical trials directed at improving the emergency care of patients with acute neurologic trauma and disease.

We commend the FDA on drafting the new guidance statement regarding the regulations found at 50.24. These regulations are critical to important life-saving clinical research, and they're absolutely necessary to protect human subjects participating in this research. Trials wishing to use emergency exception, but that do not provide adequate protection of human subjects simply cannot be allowed. Clarification of the regulation should go a long way to allowing the appropriate research, while protecting subjects.

The timing of this new guidance is really fortuitous. Recognizing the high mortality and morbidity of

medical emergencies and the paucity of research to improve the treatment of patients with critical illness and injury in the emergency department, the NIH and other agencies have recently funded three new clinical research networks to address these concerns. It's expected that all three networks will conduct some trials that can only be accomplished with emergency exception to informed consent.

As I mentioned, I represent NETT, a network funded by the NINDS to find better ways to treat intractable seizures, ischemic stroke, traumatic brain injury and spinal cord injury, brain hemorrhage, infections such as meningitis and encephalitis, and other conditions that present to the emergency department. We are here today with representatives from the other two emergency networks, ROC and PECARN, that you've already heard from. We've worked together to provide coordinated commentary and suggestions regarding the proposed guidance. We support the statements of our colleagues in the other networks, and we'll avoid duplicating the important points in their presentations, in our presentation.

The purpose of the new guidance document is to

help potential subjects, investigators, IRBs, and regulators reach a common understanding of the rules. The posted draft guidance goes a long way to achieving that purpose. In a number of areas where the regulations are quite vague, the guidance provides specific examples. To its credit, it's also very clear that these are meant to be merely examples and that the specific circumstances of any proposal may vary. We're concerned, however, about the possibility that some users of the guidance document may misinterpret the examples as new specific requirements. Perhaps such misinterpretations can be minimized by including in the guidance document not only specific examples, but a better sense of the regulatory intent of each provision of the rule. Guidance that provides both specific examples and the ethical basis from which it's derived is most likely to help readers of the document achieve the goal of both appropriate protection of subjects and rules that permit important advances in patient care.

In these comments we want to address five specific concerns, and in each area we'll propose both specific recommendations--and I won't read them aloud, but I've got

the specific text that we would recommend on the slides and in the electronic materials that you have--and we're going to provide an underlying ethical rationale that we feel may represent the regulatory intent of the relevant provision. The areas we wish to address include the five I've listed here: The purpose of public notification, the purpose of community consultation, the potential use of the central IRB that we've heard about earlier, the definition of "unsatisfactory," and the use of active controls.

On the purpose of public notification, public notification as a requirement in research conducted with exception to informed consent is actually likely to have multiple purposes. It's easy to mistake the most important purpose, however, because public notification in some ways looks like advertising or other forms of public service announcements used for health care advocacy. But the primary purpose of public notification is very different from that of, say, a store advertising a sale or the American Heart Association running a smoking cessation public service announcement. The purpose of the message in these examples is to affect the behavior of the recipient of

the message. When Macy's advertises a sale, they're trying to change the behavior of the ad's target, the potential shopper. They want that person to come to the store when they wouldn't have otherwise done so. In public notification conducted under 50.24, the primary purpose is transparency. By promoting transparency, public notification is primarily meant to affect the behavior of the sender of the message, rather than of the recipient. Requiring researchers to perform public notification ensures that they will not propose or perform trials that cannot withstand the light of day.

The distinction between the purpose of a store ad and the purpose of public notification has important implications. Let's consider two of these: First, the first requires a receptive audience. A Macy's ad presumably assumes that there are shoppers interested in buying chinos and they're looking for a place to do so, and they're not likely to be successful otherwise. The latter only requires the potential for or the threat of an interested audience. As long as the investigator is fully exposing her plans to the public for all to see, transparency is likely to

successfully affect the investigator and prevent her from proposing things she would be unwilling to openly champion.

As long as she thinks the public may care and pay attention, it actually matters little if they do.

Number 2, consequently, the success of an advertisement and a 50.24 public notification should be assessed differently. The adequacy of an ad is best determined by measuring how many shoppers came to Macy's after seeing the ad or by measuring how much they bought. The adequacy of the public notification effort cannot be determined by polling the public to see what they know about a project, but is rather determined by assessing whether the investigators' efforts were sufficiently public and open.

Paradoxically, the more effective transparency is at changing the behavior of the person sending the message, that is, at dissuading the investigator from proposing something unacceptable or controversial, the less likely the public is to notice, care, or react to a notification.

Let's move on to the purpose of community consultation. Community consultation is another important aspect of the regulations at 50.24, and something we've

heard a lot about and another area where the intent of the rules requires clarification in the guidance document. As the guidance document explains, community consultation differs from public notification in that it's a two-way communication process. Representatives of the community from which subjects will be enrolled are told about the project and are then asked to provide feedback to the investigators and the IRB.

The new guidance provides some important clarification on the mechanics of this process. Conspicuously absent, however, is any description of the specific kinds of feedback that should be solicited from the process. To determine the kinds of feedback desired, it is, again, important to know the intent of the process: Why require the community consultation in the first place, and what's to be gained by it? Clearly, there's an intuitive value to community consultation, but a more precise identification of its intent isn't so obvious. At first blush, one could argue that the intent is simply to gather any and all feedback, and I think the process should do that, but that's as a goal is pretty nebulous and not all

that helpful.

The intent of community consultation may also be misconstrued if one thinks that it looks like an informed consent process. Ethically, community consultation is not a community consent process. Why not? Because the informed consent process is an application of personal autonomy. The defining characteristic is that one is deciding for oneself what will happen to oneself. Although the informed consent process itself is fraught with limitations--difficulty in conveying complex information to lay decision-makers, difficulty in providing context for weighing risks, difficulty in assessing coercion and decision-making capacity, et cetera--these are all outweighed by the value we place on patients being their own deliberative decision-makers. When patients cannot choose for themselves, we sometimes allow a surrogate decision-maker based only their special personal knowledge of the individual person's desires. A community discussing issues in the abstract, by contrast, cannot have personal knowledge of the desires of any specific anonymous future subject and cannot represent the personal autonomy of subjects. Therefore, the community

cannot provide consent.

On the other hand, the community can be extremely valuable in sharing the values and context that are prevalent in its members. It's been suggested that one of the things defining a community is the narratives that they share. Such stories-- either factual, like shared histories, or lyrical, like share lore and mythology--may be useful in informing decision-making in emergency research with exception to informed consent. This kind of emotional and cultural context should be the primary feedback sought during community consultation. It's this information that is difficult for investigators/regulators to obtain in any other manner. An element of the research taken for granted by investigators may resonate surprisingly very strong in a potential subject's community because of a shared emotional memory. In the recent Polyheme trial controversy, for example, it's been argued that the fear of being deprived of the life-saving properties of blood transfusion was hyper-acute in the African American communities because this had been a prior common manifestation of bigotry in the U.S. It's easy to imagine that investigators may not have been

thinking about this historical context when planning the trial. Ideally, community consultation should have alerted investigators to the special sensitivity of this concern, which they can address then in a number of ways. A key response might simply be the honest acknowledgment and validation of the community's concern by the investigators and regulators, which itself is a manifestation of the respect of human subjects and a building block for trust. Investigators may have added explanations that the life-saving properties of blood were thought to be related primarily to hemoglobin and that no one would ever be deprived of transfusion of hemoglobin, and that the protocol could have been revised to state that more clearly. It's likely the community objections can be addressed by acknowledgment and validation, by supplemental explanation and clarification, or by revisions to the protocol. When they can't, investigators or regulators should decide not to conduct the trial in that community or not at all.

Potential use of a central IRB. Evaluation and approval of a clinical trial to be conducted under Section 50.24 requires effort and expertise that is above and beyond

that readily available for many local IRBs. As a result, there's concern that application of the rules may be inconsistent from one institution to another and that this variability is counter to the interests of human subjects' protection. A recent editorial in the American Journal of Bioethics suggested that reviews of applications with exception to informed consent require special expertise and more uniform application. The new guidance should be conducive to initiatives addressing these concerns.

Three multi-center clinical networks, as I said, have recently been created to study emergency therapies in different types of critically ill and injured patients. NETT, ROC, and PECARN are all developing and will continue to develop studies that cannot be completed without exception to informed consent. This increasing number of studies with exception requiring review poses both challenges and opportunities to our national and regulatory environment. The need for a strategy to optimize the protection of human subjects in these trials is imperative.

The essence of the concerns regarding inconsistent review and insufficient expertise on a local level are not

new. The National Cancer Institute Armitage Report in 1997 recognized that participants in large federally funded oncology trials were subject to "inconsistency and potential inequities in the quality of IRBs across the United States," and subsequently proposed that the National Cancer Institute central IRB be created as a solution. The report concluded that a CIRB would "assure that all patients are treated equally, and are provided with the opportunity to participate in research in institutions close to their home." It was felt that a central IRB would be the best way to ensure that subjects enrolled in the trial conducted around the country had the benefit of equal, expert, and high-quality IRB review of the trial proposal, while preserving the local review of local context. This solution has a similar potential benefit to patients enrolled in large multi-center trials using emergency exception.

The proposed guidance specifically allows for the use of a CIRB, but it has been construed by some as discouraging its use. We agree with the proposed language that local context issues are critical to review of applications with exception to consent for emergency

research and that an IRB with knowledge of the local community must review these applications. In fact, the centralization of the primary application would free up substantial resources of the local IRB, allowing for better local review. The guidance should therefore be clearly compatible with the possible future efforts at NIH or elsewhere to improve the protection of human subjects through a centralized review, providing that (1) participation is voluntary on the parts of local IRBs, and that (2) the process is approved by the OHRP and the FDA.

Talking about the definition of "unsatisfactory."

Interpretation of 21 CFR 50.24 has sometimes been difficult in part because of the relatively little guidance in defining the regulation's terms. Exception to consent is only permitted, for example, when the available treatments for life-threatening conditions being investigated are "unproven or unsatisfactory," as we've heard earlier, but how does one define "unsatisfactory" in this context? Although this was identified as a question to be discussed in the notice of the hearing, the proposed guidance does not attempt to define the term so far. We propose an

operational definition formed during the conference we heard about earlier, the Ethical Conduct of Resuscitation Research conference in New York City in May of 2005. The conference, which included physicians, regulators, administrators, and ethicists, felt that a very narrow definition of "unsatisfactory," in which the presence of an active control is indicative of a current satisfactory treatment is unjust because it excludes many patients with life-threatening conditions whom the regulation is meant to protect.

Divining the intent and ethical basis of the regulation provides a more robust and useful definition of "unsatisfactory." The working group opinion was that "existing therapies should be construed as 'unsatisfactory,' even if partially effective, when serious risk of morbidity or mortality remains, even with the best available treatment or when the adverse effects of the best available treatment are serious."

It was felt that the regulatory intent and definition of "unsatisfactory" is meant to be more than equipoise, but is meant to exclude studies where no improvements in outcome are proposed, that is, comparisons

of one satisfactory treatment versus another satisfactory treatment. In defining "unsatisfactory," the conference also found that it is not appropriate to conduct research with emergency exception from informed consent to prove that an experimental therapy is just as good as an existing therapy. The research must have the prospect of benefitting the patients and society. The conference noted that existing therapies may be unsatisfactory even if effective, if they are associated with significant adverse effects or toxicity or if they have substantial disadvantages, such as prohibitive cost or limited availability.

So, study design and the use of active controls, our last point. Study design must be carefully considered in trials under Section 50.24, particularly with regard to the use of active controls and placebo treatments. This has been addressed in the proposed guidance, but requires some further clarification. The guidance points out several possible designs, the most common design. (Buzzer) I just have a little bit more. The guidance acknowledges various situations where an element of standard therapy is unproven or unsatisfactory. A third design, one with active

controls, is implied by the first two, but not explicitly described in the guidance. When therapies are mutually exclusive, then they should be (indiscernible). That's in more depth in my paper.

In conclusion, I think that our recommendations that we try to focus somewhat on intent, that public notification is about transparency; community consultation is about narratives and respect. A central IRB should be permitted voluntarily and with local context review. And "unsatisfactory" means "not good enough." Alternative therapies do require active controls. And we thank you very much for allowing us to present today.

JEFFREY SHUREN: Thank you. Questions from the panel?

ROBERT TEMPLE: You did, if I understood you, you said fairly strongly that you didn't think the hope that a new therapy will be just as good as ordinarily not grounds for doing this. There should be a potential advantage. Did I understand you that you're making an exception where the available therapy, while known to be effective, has some disadvantage so that in that case as so-called non-

inferiority design might be okay to validate a therapy that was just as effective, but didn't have that disadvantage? Was that what you were saying?

ROBERT SILBERGLEIT: Yeah. The conference felt that if, say, a therapy was, had a certain degree of effectiveness, was 30 percent effective, but very expensive and not readily available to large segments of the community, for example, and there was an alternative therapy that was only thought to be also 30 percent effective, but was going to be readily available and could affect the treatment of a lot more patients, for example, that that could still be allowed.

ROBERT TEMPLE: Okay.

CATHERINE LORRAINE: I wanted to ask you a question about your views on community consultation. In light of your suggestion, that this is about narratives and values, I'm reminded of an earlier speaker talking about community consultation being used in several ways, one of which might be prior to almost, well, almost prior to the design of the trial, to determine whether it was appropriate to conduct the trial in that community at all, rather than

approaching the community with a well-designed trial and a plan. And I'm wondering if you think that the timing of community consultation should be different? I don't know if my question is clear, but....

ROBERT SILBERGLEIT: I'm not sure that the view that community consultation is about getting these intangibles, getting these notions that are hard to get any other way, trying to get how people feel and think about the issue, directly impacts on when the timing of that community consultation should be. I think that usually those feelings don't translate very directly into the protocol, for example. I think that it's hard enough to get medically trained research scientists to figure out protocol details and what exactly is worth what and exactly how much risk is against exactly what. I think that requires a lot of training, and I think it's probably not the right thing to be asking the community.

I think the thing to be asking the community is, you know, "Here's an idea, here's a concept. What are your-what's your gut reaction? What's, you know, what does this mean to you?" And I think that what you sometimes see is

very surprising because people, you know, you say, "What's wrong with this trial?" And they say, "Does that have to be blue?"--you know, sort of thing. The reactions are sometimes emotional and not directed at what you thought the hard issue was.

Is that feedback useful early? It's probably useful early. It's probably useful late. Does it have to be at a particular time? I don't think that our feelings about it are that important. I think what it does do is change how we assess the success of community consultation in that the outcome is really the process, you know? If you do a really good communication, community consultation process, it's not so much measured in how many lines in the protocol get changed; it's measured in how you reached out, and how you treated the community.

And that's a little hard for scientists sometimes because we're very tangible, you know? If we say, if we went and talked to a group, and we then come back with, you know, five recommendations that we can change in our document, we failed. And that's how we think, but I think we've got to step back a little bit and reorient how we

think because that's not necessarily the case when the goal is respect and (indiscernible), and it has to do with human relations, not specific edits in a document.

JEFFREY SHUREN: Other questions? Diane?

DIANE MALONEY: I had a question. You spoke about the, if you were--wanted to get feedback on scientific validity, you wouldn't go use the community consultation route, but I was wondering what your thought is on making the protocol available. I know earlier today we heard someone suggest that it could be made available upon request. So, if you have any thoughts on whether it should just automatically be made publicly available, available on request, or in what forum?

ROBERT SILBERGLEIT: I think--I don't think that anything that I said in these comments relates specifically to that. So, sort of separately, as my opinion separately is I think that just--I think that transparency is of value in and of itself that we need to do here and shows respect, and I think that making the protocol available generally is a good idea for that purpose. It doesn't relate to the comments I made here, but I think that, to the extent

possible, the more information that can be provided for those who are interested is a good thing. I mean--

DIANE MALONEY: I mean I think a challenge is, you know, how much information--if you want to get input and discussion, to have good discussions--

ROBERT SILBERGLEIT: I think the reality is, I think the likelihood of many people in the public going and looking at that protocol, understanding it, and coming up with some useful information that's going to be useful in feedback, I think is extremely unlikely. So, is it a very-- you know, I don't know that it's a very important, practical, key step, but making it available demonstrates something. It demonstrates something about what you, you know, how you, what you think about your information and its availability to the public, and I think that's probably more important than somebody actually looking at it and having a very detailed comment. But, you know, it also makes it available for that to happen if it should, but I think that that's unlikely to be important.

JEFFREY SHUREN: Questions? Thank you very much.

ROBERT SILBERGLEIT: Thank you.

JEFFREY SHUREN: Next I'd like to call Dr. Richard Weiskopf, Novo Nordisk.

RICHARD WEISKOPF: Good afternoon. Novo Nordisk and I thank the FDA meeting organizers for the opportunity to address the panel. We also thank the FDA for providing revision of their draft guidance for exception from informed consent for emergency research.

I come to this meeting with several perspectives. First, I represent a pharmaceutical firm, Novo Nordisk, a company based in Denmark with a major affiliate in the U.S. and committed to developing new treatments to meet unmet medical needs for life-threatening conditions such as acute stroke. Novo Nordisk has conducted several clinical trials in emergency settings, and importantly, it is a company with an exceedingly strong ethical culture and social responsibility.

I joined Novo Nordisk approximately 1 and 1/2 years ago and am a senior participant in the development programs related to emergencies, all of which were or are in Phase 2 or Phase 3 clinical trials. Some of you know me from my former role as a professor of anesthesia and investigator in

the Cardiovascular Research Institute at the University of California-San Francisco, where I designed and conducted a number of clinical trials in all phases, 1 through 4, as sponsored by the university, the NIH, various academic and professional societies, and by industry. During that period, I also consulted for several pharmaceutical and biotechnology firms, among other things, providing advice regarding programmatic and clinical trial design. I have served on DSMBs and IRBs. While at UC-SF, I had been a member of one of FDA's advisory committees and have been an invited speaker or member of expert panels at NIH and FDA meetings.

Third, during my years in the U.S. Army, I was manager of the Army's research program for the combat-injured casualty.

Fourth, I come as physician, dedicated to the healing and well-being of people and improving the human condition. To that end, I spent more than 35 years in clinical practice. Many of those years were at San Francisco General Hospital, treating many patients in an emergency setting.

Finally, and perhaps most importantly, I come as a human being, one who lost close family members in the Holocaust at a place where egregious crimes were committed and innocent captives were forced to be research subjects against their will.

We recognize the appropriate strong ethic of informed consent for medical treatment and the even stronger ethic for informed consent for subjects participating in research in the U.S. We are aware of the improprieties that have occurred in the past in the conduct of human research, both within and external to the U.S. Responses to some of these immoral transgressions committed in the name of research led to the Nuremburg Code, the Declaration of Helsinki, the Belmont Report, and a multitude of regulations in many countries, such as those found in CFR.

We further recognize that the FDA is the guardian of public health with respect to drugs, biologics, and medical devices, and that embedded in this responsibility is the necessity of achieving a sometimes difficult balance between permitting research aimed at improving the human condition, while at the same time seeking to minimize the

risks to those exposed to the as yet unproven pharmaceutical or device. This balance is generally more difficult to achieve in circumstances of medical emergencies. Similarly, planning for and conducting trials in this environment can be exceptionally challenging. Novo Nordisk has conducted several clinical trials in emergency medical conditions: traumatic brain injury, spontaneous intracerebral hemorrhage, and severe trauma.

We very much appreciate the FDA's expanded clarification in the current draft guidance to exception from informed consent. My comments in part are based on Novo Nordisk's practical experience in six completed Phase 2 trials and three ongoing Phase 3 trials in these emergency medical conditions, and our extensive discussions and interactions with experts in these fields. The other perspectives I outlined earlier have also contributed to the views I express today.

Novo Nordisk and I take the issue of fully informed consent extremely seriously. We support the need for DMC, an independent IRB, with concurrence of a licensed physician, efforts to contact legally authorized

representatives and family members, obtaining informed consent where possible, and community consultation and disclosure of plans before initiation of research and results following the conclusion of the research.

Nevertheless, we have some comments regarding some interpretative issues that affect trials in both efficacy and safety of drugs, biologics, devices to be tested. I will highlight some of these issues with examples from Novo Nordisk's development program. However, we believe that these apply more broadly.

In relationship to questions 1 and 2b posed by the FDA, 21 CFR 50.24 states that a criterion for exception to informed consent is that the human subjects are in a life-threatening situation and participation in the research holds out the prospect of direct benefit to the subjects. The current draft guidance indicates "trials that have morbidity endpoints, rather than mortality endpoints, can meet the requirements if subjects are at risk of death from the condition and severe morbidity that is closely associated with mortality is being evaluated."

The addition of morbidities as endpoints is

necessary and welcomed. Not permitting endpoints other than mortality is to negate the value of any therapeutic that does not decrease mortality. We believe that is too narrow an interpretation with a potential for denying patients therapies that might be of other substantial benefit. However, we do not think that the current revision moves sufficiently far from the mortality-only endpoint.

Insisting on a close association of morbidity with mortality presents some serious drawbacks. The term "close association" is not defined, leaving room for substantial differences of interpretation, making both contemplation of and agreement on design of studies problematic and, in practical terms, may do little to permit access to potentially beneficial new treatments for desperate patients and to enhance research programs in this under-researched field. Thus, we think that reduction of substantial morbidity alone should be sufficient as an endpoint. The morbidity should not be required to be in close association with mortality.

Additionally, substantial direct benefit can accrue to the participant with endpoints that differ from

mortality or even severe morbidity.

For example, providing hemostasis following severe trauma is a benefit in a variety of ways other than reduction of mortality or morbidity in close association with mortality.

Transfusion is associated with long-term immunocompromise.

Decreasing transfusion decreases this risk. However, it would not be practical to evaluate the long-term benefits of reduced immunocompromise with a randomized blinded trial in these patients. Similarly, decreasing transfusion decreases other transfusion-related risks, such as transfusion-transmitted pathogens and transfusion-associated lung injury, although here, too, because of the low incidence of these events, it would not be practical to conduct a randomized prospective trial with these events as the primary outcome measure. More rapid or definitive accomplishment of hemostasis also conserves blood components. Regional shortages of erythrocytes are well-known to physicians, the FDA, and the public, the latter through educational campaigns and pleas when shortages occur.

Perhaps less well-known is the not infrequent

shortage of platelets. At times there are insufficient platelets available to treat a specific patient who could be a trial participant, and treating a trauma patient appropriately sometimes uses the entire platelet supply of a hospital, city, or geographic area, precluding providing adequate treatment of others requiring platelets. I was an attending physician at the UC-SF blood bank for 2 years, and there were many times when it was unfortunately necessary to adjudicate the distribution of platelets to determine to which patient platelets would be allocated and which patients would be deferred for a later time.

Hemostasis also enables better surgical vision, thus allowing for better or even otherwise impossible correction of the underlying pathology. However, this subjective endpoint would also not qualify under current guidance. Nor would another benefit of improved hemostasis, physiologic stabilization of a patient allowing for transportation of a trauma victim from a community hospital to a trauma center. It is well-known that care of traumatic injury at a level 1 trauma center improves care and mortality. However, it would not be possible to design a

trial with an endpoint related to the ability to transport a victim of trauma.

Furthermore, although provision of hemostasis may improve mortality or severe morbidity, neither are closely related to the mechanism of action of a hemostatic agent. The aim of treatment of bleeding is to stop the bleeding. Requiring an endpoint so distant from the physiologic action is not realistic. This issue could apply to other potential therapies in an emergency setting.

In relationship to question 2c posed by the FDA, we welcome the FDA's guidance regarding practicability. Almost definitionally, in the defined life-threatening situations with a possibility of providing direct benefit to the subject, almost any delay in therapy--should the proposed therapy, of course, prove effective--will result in a decrease in efficacy, thus providing an unnecessarily artificial difficulty for a trial.

Here, too, "unduly delayed" allows for substantial interpretative differences. For example, hematoma volume following spontaneous intracerebral hemorrhage increases during the first 3 or 4 hours following the initial

hemorrhage, with neurologic outcome strongly related to the ultimate size of the hematoma. Thus, any delay of therapy providing hemostasis for this condition decreases the efficacy of that therapy and thus the direct benefit to a subject participant. Withholding an effective agent for the 45 to 60 minutes required to obtain a properly informed consent will result in the patients in the trial having inferior outcomes to those treated post-licensure in clinical practice and, in the worst case, could result in the failure to reach a positive trial outcome for a devastating disorder with no other effective treatment. The definition or interpretation of "unduly delayed" must not permit an adverse impact on efficacy or safety.

Similarly, issues related to practicability impact trials in trauma. Trials designed to detect significant reduction of either morbidity or mortality following severe trauma require a large sample size. Despite worldwide enrollment in many trauma centers, the trials will be so lengthy as to threaten the practicality of the trial and the meaning of the results because medical care will likely have changed during the lengthy duration of the trial. Planning

such a trial and interpretation of the results becomes nearly impossible. For example, most traumatologists would regard reduction of mortality following major trauma from 30 percent to 25 percent as highly medically significant. However, a trial with a power of 80 percent to detect this difference with an (indiscernible) of 0.05 would require nearly 2600 patients. Ninety percent power, which is not unusual for a Phase 3 trial, would require more than 3400 patients.

These sample sizes in this emergency environment are unrealistic in terms of numbers of patients to be enrolled if those unable to provide full informed consent cannot be included. For example, our current clinical program in trauma being conducted throughout the world, including the U.S., at more than 100 trauma centers is expected to require approximately 4 to 5 years to enroll 1500 patients. In the U.S., we're able to enroll only a small fraction of those potentially eligible for the trial owing to their inability to give informed consent because of their severe medical condition, the very condition that we seek to treat. These patients arrive at a medical center

most frequently without family members who could provide assent for the patient's enrollment. Enlarging this trial to 2600 or 3400 patients would require 9 or 11 years. Trials of such exaggerated duration not only tear at the meaning of "practical," but such an undue delay could produce results of uncertain meaning owing to the trial's duration. It is clear that these issues are a major reason for the extremely limited number of substantial trials and therapeutic advances in this field.

In relationship to question 3 posed by the FDA, we welcome the FDA's recognition that these unfortunate patients unable to give consent owing to their disorder are highly likely to have a more severe form of the disorder than those who are capable of providing consent. We have serious doubt that data from these less severely afflicted can, with any reasonable assurance, be extrapolated to those with the more severe form of the disorder. We believe that this may apply not only to data regarding efficacy but to that related to safety as well. An issue of concern to us is that, following approval of such therapeutic, physicians are highly likely to use it for those patients with the more

severe form of the disorder, for example, unconscious trauma patients in whom safety would not have been established. For example, what might the effects of the more profound shock and/or tissue damage be on the safety of the therapeutic to be tested? Should not the answer be known before rather than after approval? Although I wrote the submitted abstract containing these thoughts before the recent IOM report, I draw your attention to that report, perhaps unnecessarily, in that the IOM addressed the important issue of drug safety and discussed the problem of adverse events that are discovered after drug approval.

In relationship to question 2b posed by the FDA, we suggest that appropriate consideration and interpretation be given for those proposed trials in clinical, life-threatening situations where adequate pre-clinical models do not exist despite appropriate efforts.

In summary, we share the common goal of improving opportunities for survival and reduced morbidity for patients in emergent life-threatening states, not at all costs, but with appropriate ethical controls and actions. Of course, we are completely in accord with the requirement

for informed consent where possible. As does the FDA, we, too, recognize that for the public good and potential benefit of trial subjects, for the treatment of emergency disorders, under some circumstances, an exception is necessary. We believe that less limiting study endpoints should be permitted, that in evaluating requests for exception to informed consent, substantial consideration be given to improving the evaluation of both efficacy and safety of pharmaceuticals by removing barriers to inclusion of those more severely afflicted and thus are unable to give informed consent. One might take the view that to do otherwise is not ethical.

One should not construe FDA inaction on this point as adherence to the principle of first do no harm. Harm can and has ensued as easily from inaction, as noted by a previous IOM report, as from inappropriate action. We also suggest that the requirement for pre-clinical studies be rephrased to take into consideration those conditions where appropriate pre-clinical models are not available.

I came to these comments and conclusions after a professional lifetime of experience in clinical research,

both in academic and industrial environments, many years of experience caring for patients with these conditions, experience as an expert for the NIH and the FDA, and as a human to whom inappropriate research in humans is deeply abhorrent. Thank you.

JEFFREY SHUREN: Thank you. Bob?

ROBERT TEMPLE: The language about linking the morbidity to the thing that's threatening the patient's life allowed us to write guidance without changing the rule. Okay? So, I need--I think we'd like to understand a little more what you think the problem is with the resolution to that issue that was, that appears in the guidance. The guidance was intended to say that if the thing you're treating has both mortal and serious morbid consequences, it's okay to have the trial designed to decrease the morbid consequences, you know, the amount of intellectual function left or something like that, as long as the stroke is life-threatening in the first place. I think the reason for demanding that it be life-threatening was that it's a big deal not to get consent. So, we wanted a high threshold.

Say a little more about what impediment you feel

that places on doing the right kinds of study. I didn't quite get that.

RICHARD WEISKOPF: Sure. Okay. I fully--I understand and appreciate the difficulty you face here, but let me take an example of something that I didn't mention, which dissociates the morbidity from a threatened mortality, and this is clearly hypothetical: Suppose, for example, somebody is inebriated and gets into an altercation with somebody and has developed--gets punched in the eye and has an open eye injury and has lost vitreous, and the potential result from that is great loss of vision or maybe even complete loss of vision. And yet, it is--the basic underlying problem of the person's inebriation is unlikely to be one where he or she faces mortality. The eye injury is unlikely to be one that he or she faces mortality, and yet this is an issue that probably most of us would say, "I'd like to get this fixed right, and anything that you can do that might advance that would be a potential benefit to me."

ROBERT TEMPLE: Okay. So, in this relatively unusual case, the reason the person can't give consent isn't

that he had a terrible head injury; it's that he's drunk.

RICHARD WEISKOPF: Well, in that instance, yes, but you could just as easily say that he was in an automobile accident, had a head injury. The head injury might not be sufficiently severe to create an imminent threat of mortality, yet it would be severe enough to impair the person's mentation and ability to give consent, and you have the very same issue.

ROBERT TEMPLE: Okay. Fine. That's helpful.

JEFFREY SHUREN: Other questions?

ROBERT TEMPLE: Actually, I had another one. "Practicability" is the term that's used to described whether you can get the same information from another environment, people who aren't as sick or anything like that. I think our thought was that if someone could say, "Well, yes, I could do the study in these less ill people, but I wouldn't get the answer," that would be the answer to practicability. Then you'd say, "Okay. Now I've shown that it's not practicable to do the study I need to do in that population. I won't get the information I want." But you appear to have a problem with that. If you could clarify

that further.

RICHARD WEISKOPF: Sure. Well, it may be an issue of interpretation and the intent of those who wrote the guidance versus those such as myself who are reading the guidance. And as I and others who have read what is written, that doesn't--what you seem to say did not come through clearly, that if one can enroll patients with a less severe form of whatever it is you're seeking to treat, then that would be okay, but that leaves out all those who have the more severe form who may not be able to give consent because of their very disease process. And I have issues with respect to both efficacy and safety for those patients who surely will be treated post-licensure, should the therapy be effective and licensed.

ROBERT TEMPLE: Yeah. Okay. I don't think that sort of answer wouldn't be acceptable in terms of what we asked, but if it's not clear, then perhaps we need to clarify it.

JEFFREY SHUREN: Denise?

DENISE ZAVAGNO: I also had a question about practicability. In your talk today, you were explaining

that in trauma trials it can take sometimes, you know, 4 to 5 years to enroll 1500 patients, and that just isn't practicable. So, you looking to us for some definition of "practicable" that would somehow encompass that, and I'm turning it back to you, is there some length of time in which you think a trial becomes impracticable? Is it 2 years? Is it 3 years? And is there some other definition you could help us--provide us with?

RICHARD WEISKOPF: Well, it's a combination of many things, and I don't think I can give you an absolute one-number answer, but perhaps I can give you the thoughts that guide what gets one to an answer. And one wants to be reasonably confident that medical therapy for that condition would not otherwise change substantially during that period of time which would threaten to negate the entire study, that if the patients treated at the beginning of the study in fact have the standard treatment different towards the middle or the end of the study, one wonders what the study is all about when it's over.

Second, in terms of getting a study just done on a practical basis, when one looks at creating a study and the

logistics and the funding of a study, getting out to 4 or 5 years is pushing the envelope. That is probably actually beyond what most or many, I won't say "most," but what many funding agencies, including industry, would say, "This is beyond reason and in terms of life cycle of a product, in terms of the cost, is beyond what we are willing to undertake." We are undertaking that, but it is, I think, at the very edge of what people are willing to undertake.

DENISE ZAVAGNO: Okay. Thanks.

JEFFREY SHUREN: Any other questions?

DIANE MALONEY: Yes. I had a question. I wanted to just get your take on public discussion, say, at an advisory committee, on these kinds of studies to get both scientific and ethical input on the protocol or on the, you know, the issues surrounding community consultation.

RICHARD WEISKOPF: You're talking about an FDA advisory committee?

DIANE MALONEY: FDA advisory committee or we've heard other discussions, but I'll ask it specific to an FDA advisory committee.

RICHARD WEISKOPF: Okay, and this will clearly be

my personal view, not representing anybody about this. I don't believe that, as currently constituted, those committees are appropriate for that task. I think that to undertake that task would require different constitution of committees.

DIANE MALONEY: If you had a committee that was constituted appropriately, what value would you see in having a public discussion of these studies?

RICHARD WEISKOPF: Are you saying a mandatory discussion of every such study that is submitted for approval or are you talking about selected studies--

DIANE MALONEY: Well, let's start with selected. And ones, let's say, that seem to raise specific issues of concern.

RICHARD WEISKOPF: Well, I think the advantage is then similar to the advantage that accrues to other reasons for which various groups within the FDA bring things to their advisory committee, that is when they need advice about a specific issue which may, they maybe internally cannot agree or don't feel they have appropriate expertise, even with some outside consultation, or they want to have a

public airing for any reason, one reason or another. So, those very same advantages would accrue to this issue as well for selected studies.

DIANE MALONEY: Right. And any concern, though, about having the discussions being in a public forum?

RICHARD WEISKOPF: I think one can do it in a way that it's done not too dissimilarly from currently where there could be an open session and then, as necessary, a closed session to discuss proprietary information.

DIANE MALONEY: Right. I guess that goes to, I think, some of what we've been hearing today. I think I've heard a number of people say the protocol ought to be made publicly available, and right now the, you know, the way it works is those are considered protected, confidential (indiscernible).

RICHARD WEISKOPF: I have another issue, other than the protected proprietary information that a, if somebody's going to spend a huge sum of money trying to institute a protocol, to then suddenly have it open to, sort of and lose that intellectual property is an issue of intellectual property rights, and whereas I'm not an expert

in that, I don't seek to hold myself out as that. But there's another issue as well, and I think analogous to patient care. If a patient asks me about a specific procedure, I wouldn't just hand that patient a bunch of reprints or a textbook and say, "Here, read about it. It's open literature." It would be in the context of "Let's have a discussion about it, and I'll talk you through it, and we'll go through every point. We'll talk about it as long as we need to talk about it to make you understand." But this pile of information, unless you're an expert in this area, is not going to be particularly useful to you and, in fact, might be detrimental.

And so, I would take the same approach with a research protocol saying that, for the vast majority of people, this would not be particularly useful without an explanation, an in-person explanation that goes along with it, to guide them through it and explain the risks and the potential benefits.

DIANE MALONEY: I have just one other question, and I'm sorry. I don't mean to put you on the spot.

RICHARD WEISKOPF: That's okay.

DIANE MALONEY: I just really appreciate--

RICHARD WEISKOPF: That's what I'm here for.

DIANE MALONEY: --having a sponsor here. I, you know, of course, I think most of us have noted that we've had mostly emergency researchers here, and I was trying to figure out why that was, and I think those are the people who are in the trenches and really dealing with the patients and trying to say, "What can I do?" and probably frustration in not having medicines to be able to treat the patients that they see.

So--but it's really important to have the sponsors', you know, multiple sponsors' perspectives as well as patients' perspectives, and I know that we're getting that in the docket, and I expect we'll get a lot more of that as well. But I would ask if you could comment on what role you think the sponsor or sponsors can play in working with researchers and IRBs with regard to these kinds of studies.

RICHARD WEISKOPF: Well, of course, sponsors work with investigators very closely. It does neither the sponsor nor the investigator nor the study nor the proposed

therapeutic any good whatsoever for a sponsor to propose a protocol that an investigator's not interested in pursuing for various reasons, and so the protocols are arrived at in very close consultation between investigators, the various experts, external expert advisory committees, and internal discussions, and what comes out is, rather than a sharp cube, somewhat of a rounded marble that presumably satisfies--if it doesn't completely satisfy everybody's needs, at least it's a reasonable compromise and gets at the goal.

I'm sorry your second part of your question?

DIANE MALONEY: It just had to do what role the sponsors can play?

RICHARD WEISKOPF: Oh, with IRBs. Now, traditionally sponsors have had an arm's length from IRBs, and the investigator has been the intermediary, and that has been the way IRBs have wanted it. To do otherwise would require a sea change in the culture of the way IRBs and universities and investigators work. The various IRBs that I've participated in and have presented as an investigator as well would be, I would say, would be loath to have direct

interaction with the sponsor.

DIANE MALONEY: Thank you.

ROBERT TEMPLE: Just returning to the availability of the protocol. A number of people who spoke earlier thought that a protocol for any one of these kinds of studies ought to be available. There are pieces of legislation and the IOM committee report, all of which say that any study, being any Phase 2/3 study anyway, out to be available on some kind of registry. They don't necessarily insist that the protocol be available, although if I were them, I would, because you really can't tell from a brief summary.

But leaving that aside, I think the contention of people here is that in this rather sensitive setting where people are not going to be given consent, it's more important than ever to convey a sense of openness so that, even though I'm sure you're correct, most people can't read a protocol properly, this would be available for them to read if they wanted to or they could find a local expert who could read it to them or something like that. Do you think that's a problem for people designing studies? I mean it's

not really true that these things are secret. All the investigators know the protocol, you know, any decent reporter could find it out easily. How important is that?

RICHARD WEISKOPF: Well, yes, and investigators do know the protocol, but if you go to a community where there's been--and we've heard testimony about that, not "testimony," but presentations earlier today, that if you go to a community where there has been "community consultation" about a protocol and you randomly ask people, the odds in finding somebody that (1) know that the research is going on, or (2) truly understand what it's about, is pretty low.

But even if you took a protocol--

ROBERT TEMPLE: We let people vote, you know. They don't have to pass a test first.

(Laughter)

RICHARD WEISKOPF: You don't want me to comment on that, do you? (Laughter) But if you take--the purpose of having a protocol available presumably would be to impart information, and if it does not achieve that objective, then what is the point? If you can't achieve imparting the information correctly so that it can be interpreted

correctly, you perhaps could be doing more harm than good. And, in fact, the odds are that, for various reasons, various members of our society could well interpret these, what's written in a protocol, in a, shall we say "rather idiosyncratic way" and produce publicity or produce information that would really be contrary to either the intent or the actual methodology of the protocol.

So, I think--I'm in favor of the transparency, but I think the method of going about that, I don't believe the correct way is just to have the protocol open and available on a Web site where anybody can read it. I think it requires appropriate interpretation to the person.

Similarly, I mean, as I pointed out, the same as for clinical medicine. You want to impart enough information to a patient so that the patient does what is in the patient's best interests, can make the appropriate choices, but not so much that they are frightened away from doing what is best. And that's easily done enough.

JEFFREY SHUREN: One other question on public disclosure. We've heard from some folks an interest that the results of a trial, regardless of whether they be

positive or negative, should be made available to the public. Do you have an opinion on that recommendation?

RICHARD WEISKOPF: I think that is something that has gathered a great deal of favor in the past several years; whereas, some years ago, nobody really talked about that whatsoever. As, having been an editor of a journal and all the other things I told you about earlier, I think I come down--it's not an easy question, and that's why I'm hesitating. The question's easy; the answer, for me, is not so easy, and that's why I'm hesitating. I think I come down on the side that says, yes, that information should be made available, but, again, it has to be done in a way--it's not so easy--it has to be done in a way that can be appropriately interpreted.

But I think, especially in this environment, if we are to expose patients to research without their consent, which is a very special thing and should be done only for special circumstances, then I think we do owe society the results of those investigations and not to, if they're adverse or neutral, they don't work out, those should nevertheless be made public in some reasonable way.

JEFFREY SHUREN: Any other questions?

BONNIE LEE: There has been a lot of proposals today and presentations for either a central IRB review, a national review, a regional review, or an advisory committee type of review, but centralized. And you--I don't believe you really commented on that, and I would be interested in your views. I will add that I think there's been an assumption that, if that type of process is used, it will save a lot of time. I don't know whether that necessarily is true. I go back a long way, and remember another national advisory committee where, in fact, the researcher died before his research got through it. (Laughter) So, there are different models one can use, but as, I believe, the only sponsor here, I'd appreciate your comments.

RICHARD WEISKOPF: Well, I--please don't interpret my comments as that for sponsors at large. First, I work for only one sponsor, and I haven't been doing that for very long either. So, probably my comments probably are more heavily weighted by my 35 previous years of experience than my past 1 and 1/2. But having said that, you're right, I didn't make any comments about that issue, and that is

because (1) I wasn't aware that people were going to be making comments about that, and it wasn't an issue that I felt was one of the top several that I wanted to get across.

As you could see, I barely fit in or I was actually 30 seconds over my time limit. And so, I've only really had a chance to think about this during the presentations today, so I hesitate to give you sort of off-the-top comments about that without really working it through, but since you asked, I'll give you my first blush comments, as it were.

And (1) I don't think that it will save time. I think it will add just another layer. I don't believe that local IRBs will defer to a central IRB, and I would find it, I think--I would be surprised, shall we say, that if laws were passed that would by-pass local IRBs in favor of one central IRB. So, I would see it as a layer added above with additional time, not only for the review of that particular body, but then responses to that body. And protocols such as these rarely go through an IRB first pass, and depending on how frequently that individual IRB meets, most commonly once a month or so, if there's a second or even third set of questions, we're looking at several months of delay. Well,

this will then add additional time of perhaps several more months of delay.

And then there's a separate issue of IRBs, the several IRBs that I was involved with directly and now through sponsorship, getting a sense of many IRBs or ethical committees, as they are called in Europe, all over the world, they're quite different one from the other. Each one has--certainly there are differences in different countries, but fortunately you don't have to address that, but even within a country, especially a country as big and as diverse as the United States, they each--many IRBs have their own--I won't call them pet peeves, but their individual focuses, if you would. And one IRB might think items 1, 2, and 3 are the critical important things and pay attention to that; whereas, another IRB might say, "Yeah, 1's important. We don't care about 2 and 3 so much, but here's 4, 5, and 6."

And I think it would be logistically very, very difficult to have one central IRB or something, if you wouldn't call it an "IRB," you might call it something else.

In a way, the FDA or the NIH, when it says, "Okay, you can go ahead and go to local IRBs with this protocol," in a way

is sort of acting as a clearing house for that. They are saying, "It's good enough to satisfy the CFR, and not only the intent, the spirit and the intent and the letter, and so now take it to your IRB and see if they have any local issues that they want to deal with."

So, maybe I missed some points of what early presentations had to say, but I'm not sure I see the value of this so-called central IRB.

JEFFREY SHUREN: All right. Thank you very much.

(Applause and laughter)

JEFFREY SHUREN: That ends the portion of registered presenters. There are three people who had signed up subsequently to speak. I will now ask Colonel Jerry Pierson to come forward. Again, I will allot each of these individuals 15 minutes, then questions from the panel.

JERRY PIERSON: I have a brief statement. On behalf of our commanding general at Fort Detrick, Major General Eric Schoomaker, as you know, with the Army, we're very much interested in trauma and trauma research, which is a concern for all Americans who know that we're actively engaged in a global war on terrorism. On behalf of the U.S.

Army Medical Research and Materiel Command, I welcome the guidance proposed by the agency to further explain the procedures to be followed when an exception from the informed consent requirement for emergency research is requested.

As the leader of an organization committed to developing products to provide America's military forces with the best emergency and intensive care possible, I recognize that the research community at large is in need of clear practical guidance in order to protect all potential participants in research.

Furthermore, I understand that the burden of morbidity and mortality from trauma on the American population is great, with trauma, as a leading cause of death, responsible for over 160,000 deaths in the U.S. annually. These sobering statistics underscore the reality that the products currently available do not adequately address the nation's trauma treatment needs. New technologies must be evaluated using scientifically sound methods in relevant patient populations. With clear guidance, sponsors and researchers can prepare meaningful

research protocols that appropriately address the critical priorities of informing the community and protecting potential research participants. Additionally, institutional review boards will better understand their responsibilities in reviewing protocols seeking exemptions from informed consent regulatory requirements.

Signed, Eric Schoomaker, Major General, U.S. Army Commander of the U.S. Army Medical Research and Materiel Command. Thank you. Back to you.

JEFFREY SHUREN: Any questions from the panel? Thank you very much.

Next I'd like to call Paul Knudson.

PAULA KNUDSON: I'm Paula Knudson. I've been an IRB administrator for 30 years and an IRB member for 25, and I wanted to speak to the point about community consultation and give you one IRB's experience with this kind of event.

In the first place, I want to say that back in the early nineties, when the FDA insisted that we approach the justice principle more broadly than we had been doing, the inclusion of women of child-bearing potential, ethnic diversity amongst our research subjects, and now, of course,

the inclusion of pediatric patients, we became concerned about what did our community actually think about research, and embarked on a community outreach program, in which we tried to educate various community members about what research was, and then to find out what they felt the barriers were to participation in research. We have always had a very large component of community members on our IRB and currently have 22 percent of our members who are unaffiliated and non-scientific, and we use them very broadly for suggestions for venues in which to make presentations.

So, then we came to the first time we received emergency exception to informed consent on a protocol that we had with the NIH, hypothermia and head trauma, in 1995. And I think we were the first that were told to do community consultation. It was a year before the FDA did indeed advance its rule, which included community consultation. So, we were confused about what this was and what we should do, and then it dawned on us that actually we had already the beginning of a model that we could use to achieve community consultation.

So, when we indeed have a protocol that uses the emergency exception, the IRB meets in a formal meeting to decide whether this protocol is acceptable at all. If it does, it then appoints a subcommittee to decide how many and which sorts of venues presentations should be made to elicit community response to the type of protocol that it is. And it also must determine what would be the level of positive response that would be acceptable to the IRB at another convened meeting.

So, then the subcommittee will decide maybe 14, maybe 17 places, groups that we should go to, which attempts to cross social, economic, and ethnic differences in the Houston community. I am at the University of Texas Health Science Center in Houston, and I'm sorry I didn't say that in the beginning.

A member of the IRB goes to each one of these groups, along with the investigator. The principal investigator is then permitted to outline the study, to talk about what the potential risks are inherent in the study, and what the potential benefits would be. The IRB member then explains what an IRB is, what the IRB has determined

about the study, and tries to elicit questions, concerns from the community members that are present. At the end of the question-and-answer period, I do a little spot quiz, a little written quiz, three or four questions: What are your concerns about this protocol? Do you understand that the protocol is doing this without your informed consent? Would you be willing to participate in this protocol, and do you think the members of your community would be willing to participate? And that's just to give us some tangible evidence of what went on, even though we take a sort of overall assessment of whether there is a positive response from this community setting or not.

The IRB determines about what level of positive response would allow us to proceed with the protocol, and it's usually somewhere between 87 percent positive response to 90 percent positive response, and then we would be willing to proceed. And it comes back for a final decision on the part of the IRB at a convened meeting.

And I do not think that this is either too much time or too much cost. There are few such trials, and it is essential that we do as much as is necessary to inform the

public and receive and consider their concerns. Do I think that everyone in Houston knows about every trial that we have gone out to talk about? No, of course not. But I think that by earnestly and seriously carrying out the process demonstrates respect for persons and hopefully demonstrates that we have earned the public trust. Thank you.

JEFFREY SHUREN: Thank you. Let me ask, you've had experience with community consultation.

PAULA KNUDSON: Yes.

JEFFREY SHUREN: How have you gone about notifying the public? And then when you've held one of these meetings to which members of the public have come--

PAULA KNUDSON: No, we go to them.

JEFFREY SHUREN: You go to them?

PAULA KNUDSON: Right. And I--let me tell you the sorts of places we go.

JEFFREY SHUREN: Yes, if you would.

PAULA KNUDSON: We go to breakfast clubs and service clubs. We go to neighborhood community centers. We go to health fairs. We go to churches. We go to PTAs. We

do all the hospital volunteers, the Texas Medical Center chaplains. We've done focus groups. We make presentations, not me, but on Spanish-language radio and television. I have actually been on a gospel radio program with call-in questions. I've been on a rock radio station with call-in questions. So, I mean, we do try to get out.

JEFFREY SHUREN: You had mentioned that if you get sort of 80-90 percent positive response, you'll proceed. Have there been cases where you've not gotten that level of response?

PAULA KNUDSON: No, actually not. We've done, I think it's five trials using emergency exception, and we've gone through this process five times. I'm not entirely sure why we get such a positive response. It may be all of the programs that are on television, or it may be that--even though we explain that research is being done because we don't if it will work, it may not work, it may be worse than what would be standard--people are willing to hear that there might be benefit in these dire circumstances.

JEFFREY SHUREN: And just one last question--

PAULA KNUDSON: Yeah.

JEFFREY SHUREN: --from me, and then I'll turn to others. What kind of feedback have you gotten in terms of the process you've used for community consultation?

PAULA KNUDSON: Well, we have heard that people are very grateful that we've been out there to talk to them. We continue to do the community outreach, talking about research, going to all of these places, just talking about research in general, that there are such protections for the public as an IRB provides. We hope we're providing some protections. We've never measured it, but we do hope so. So, we speak to it that way.

JEFFREY SHUREN: I'm sorry. I'll throw in one more.

PAULA KNUDSON: Yeah.

JEFFREY SHUREN: Would you now, after going through five trials, would you do anything differently in trial number 6?

PAULA KNUDSON: No, I don't think so. I think we would continue to do just more of the same.

JEFFREY SHUREN: Questions from--Joanne?

JOANNE LESS: I was just wondering, you said that

at the end, you give a quiz, and you test to see how much they understand of the trial. Do you give them written materials or just a description of the trial, a summary?

PAULA KNUDSON: Oh, yes. There handouts about the trial in general terms. If it's proprietary information, we're not talking about what the drug is made up of, but we certainly have a handout about the trial. We go over it in great depth. These meetings take at least an hour and a half. I mean we're not rushing through anything, and then we're trying to elicit concerns: Would this be appropriate in your community? And the only reason that we do the spot quiz is just to have some tangible evidence. I always bring someone along who counts noses, so that we know that there's 35 people or 135 people in the room, what sort of ethnic make-up are we seeing in that room, trying to get a handle on the different communities that make up Houston.

JOANNE LESS: And I had a second question, but I forgot it.

(Laughter)

PAULA KNUDSON: It's the end of a long day.

JOANNE LESS: Hopefully I'll remember while

somebody else is asking.

DIANE MALONEY: I had a question, just when you talked about the feedback that you get. So, in getting feedback, for instance, how do they give it? Do you ask for a show of hands "Do you support this trial?"?

PAULA KNUDSON: No. We elicit comments from people. I mean we ask them to please talk to us about what their concerns are during these meetings, and then anything that they didn't want to say out loud they can write on the little quiz. You know, "Do you have concerns that you want to share with us?"

DIANE MALONEY: Right. So--but not everyone that comes is speaking up at the meeting?

PAULA KNUDSON: Of course.

DIANE MALONEY: So--

PAULA KNUDSON: And not everyone completes the little quiz, but we get, you know, probably 75 percent of a room will do the little--they're always, I think, fairly delighted to be asked to do that. We don't have them sign.

DIANE MALONEY: Right. So, are you using the results of the quiz then to come up with your 87 to 90

percent?

PAULA KNUDSON: Well, the result of the quiz and sort of a general consensus of what the room was like. Was it a positive sense? Or was it--were people really saying, "Oooh, I don't like this. You're denying me a basic right that I have to give consent"? You know? If you hear things like that, you know that someone's not very happy.

DIANE MALONEY: And have you found that, say, the number of people coming, that you have more interaction in smaller size groups, larger size groups?

PAULA KNUDSON: Well, I don't like the 135-size group as much as I like the 35-size group.

DENISE ZAVAGNO: You said that your IRB forms a subcommittee, and then the subcommittee decides where you're going to do the outreach and how many places you're going to go? Do you base the number of places you're going to go on the seriousness of the trial, like--

PAULA KNUDSON: No. They're all treated about the same. It just sort of depends on whether we think it's going to be a more local environment or whether our (indiscernible) going to be going out to 13 different

counties.

DENISE ZAVAGNO: Well, you said you go to 14--

PAULA KNUDSON: Somewhere between--

DENISE ZAVAGNO: So, it's not based on level of risk at all?

PAULA KNUDSON: No, it's not the level of risk. We treat them all as being high risk.

DENISE ZAVAGNO: Okay, and you said you normally go out to 14 to 17 places?

PAULA KNUDSON: Right.

DENISE ZAVAGNO: And who picks those places? The subcommittee?

PAULA KNUDSON: The subcommittee members help us. We call, we get on the telephone. We call all these groups, and we ask them whether they would allow us to come to make a presentation about emergency research.

DENISE ZAVAGNO: Okay, and say you go to a place and you can feel in the room that it's kind of negative? People are saying, "Oh my, I don't want this in my community. I don't want this to happen." Do you change the way that you do your presentation for the next time--

PAULA KNUDSON: We try--

DENISE ZAVAGNO: --to try and incorporate what their concerns were?

PAULA KNUDSON: Absolutely. Absolutely.

DENISE ZAVAGNO: But wouldn't that change?

PAULA KNUDSON: No, I don't think so. I think it helps us to find out, you know, is this reflective of this community, which is so hard to define because Houston's got about 3 million people in its greater statistical setting. I mean it's just very large and very diverse. We try to incorporate what everybody says to us.

DENISE ZAVAGNO: Well, have you ever gone back to the investigator and said, you know, we've had so many negatives here, we think this trial is a no-go?

PAULA KNUDSON: Yup, we have indeed. We have indeed. Just once.

JOANNE LESS: I remembered my question, and actually Denise asked it. It was whether or not you do take into account the incremental risk, and it sounds like you don't, but--

PAULA KNUDSON: We just treat--any time you are

not obtaining informed consent in a life-threatening circumstance, that's high-risk research.

JOANNE LESS: Okay. So, would the--

PAULA KNUDSON: Whether there's--

JOANNE LESS: With regard to the AHA proposal then, now that you've heard that discussed today by a number of people, do you have any thoughts on that? Do you still--

PAULA KNUDSON: No, I'd rather not--

JOANNE LESS: --do it the same way?

PAULA KNUDSON: I'd rather not comment on that one.

JOANNE LESS: Okay.

BONNIE LEE: I had a follow-up to Denise's question. Paula, when you said that you were getting comments at all of these different venues and you had done this for five studies--

PAULA KNUDSON: Hmm-mm.

BONNIE LEE: And you indicated to Denise that you had, based on public input, decided not to do at least one of those. For your other studies that you did permit to proceed, from the public discussion, did you change the

protocols in any way in any of the studies? I mean, was there tangible results?

PAULA KNUDSON: No, we changed the way we wrote some of the public disclosure pieces that we put into the newspapers, and I think we just emphasized a few other points. Yeah.

BONNIE LEE: Thank you.

PAULA KNUDSON: The protocols were really not changed.

BONNIE LEE: Well, I would assume that's because you do a pre-review--

PAULA KNUDSON: Oh, yeah.

BONNIE LEE: --by the IRB, and therefore you feel the protocol is--

PAULA KNUDSON: Is acceptable. Right.

BONNIE LEE: --is acceptable. I see.

PAULA KNUDSON: Exactly.

SARA GOLDKIND: I have a couple of questions.

PAULA KNUDSON: Yeah.

SARA GOLDKIND: One is, I'm wondering if off the top of your head you could say how long roughly it's taken

the IRB to review these five protocols, say, from soup to nuts, from the beginning with the pre-review and then at the end, after the community consultation process has gone through.

PAULA KNUDSON: I think it's a minimum of 5 months, and it's sometimes longer.

SARA GOLDKIND: And the other question I had is, we heard today that there are--some people have experience that-- (Buzzer sounds) Some people have experience that it's more successful to go out to pre-formed groups to do the community consultation process, rather than bringing folks into the hospital setting for group-specific meetings, specifically related to the protocols. I'm wondering if you have any comments on that based on your experience.

PAULA KNUDSON: Well, I've never been particularly keen about the idea of having community representatives come on some sort of community advisory board, because I think within a very short period of time they become institutionalized, you know. I think we should go directly into the community, into these churches and into the health fairs, you know, where people just show up. People, the

ordinary folk, arrive, and we get a chance to talk to them.

They're not the gatekeepers for the community.

SARA GOLDKIND: And you mentioned that you've done focus groups.

PAULA KNUDSON: Yeah.

SARA GOLDKIND: How successful did you find that venue?

PAULA KNUDSON: Well, for instance, when we started doing pediatric research, well, it wasn't for emergency exception, but we did a lot of focus groups with parents of children, members of the IRB as well as members from the community in general, just to talk about children, children's research and the issues. There are so many.

SARA GOLDKIND: Thank you.

DIANE MALONEY: In preparing the materials for community consultation, in general, your experience--has the researcher prepared those or the IRB or done together?

PAULA KNUDSON: It's done together.

DIANE MALONEY: Together?

PAULA KNUDSON: The researcher will present the handout about the study, which the IRB will take a look at

to be sure it's not weighted too heavily on the benefits side. And then, the IRB member or members that go usually have a tailor-made presentation about what IRBs are, the fact that, you know, the bedrock for all research is informed consent, and we're denying you the opportunity to give you your informed consent for this study. I really lean very heavily on that because I want people to really understand.

DIANE MALONEY: And how important do you think it is that an IRB member be there for the community consultation?

PAULA KNUDSON: Oh, I think it's terribly important. I really do. I think it's, it otherwise is all one-sided, if you will. It's too uneven an exchange. Researchers do the research because they really believe in it, and they can easily communicate that. And the IRB member has to put the brakes and say what the real, you know, that informed consent is being denied, that there are risks in this study, that we need your input before we can decide to do this, and it's a more balanced presentation.

DIANE MALONEY: What's your sense of other IRBs in

terms of going out and participating in the community consultation?

PAULA KNUDSON: I think we're a very rare IRB that does this.

DENISE ZAVAGNO: Since you've gone out and met with the communities and heard their questions, I'd like to hear what you think about the opt-out provisions that have been in place in some trials and whether or not you think that the community likes those or whether or not you think they're necessary or if they're feasible.

PAULA KNUDSON: Well, I think it's a fiction. I think that, you know, for the Polyheme study, we did the blue bracelet. I think that people may have worn it for a month and then stopped wearing it. I think they'd forget that there's an opt-out provision. I think if somebody really didn't want to be, I'd want it on their driver's license, somewhere in their wallet, in big red letters. I just--I don't know the best way to do opt-out. Just not do the research.

CATHERINE LORRAINE: I just wanted to ask one other question. When you all go out and do this

consultation, is it usually one member of your IRB plus the investigator?

PAULA KNUDSON: Yes. Yes. Usually.

CATHERINE LORRAINE: Thank you.

DIANE MALONEY: I'd like to ask--

PAULA KNUDSON: (Indiscernible)

DIANE MALONEY: Oh, I'm sorry. Sorry.

PAULA KNUDSON: That's all right.

JEFFREY SHUREN: Go ahead.

DIANE MALONE: In terms of the experience you've had, what changes have you made over time that you've learned, you know, from hearing from the community what it is they're looking for? Are there specific things you could point to that you could say, sort of generalize, that you noticed that they really wanted to know about this or that?

PAULA KNUDSON: People really seem to want to know what the state of the art is. What's the realistic happening in an emergency room when your brought in with a head trauma? That's what they really want to know. And, is what you're planning on doing going to attempt to make better treatment for them? They're really interested in

better treatment for what's going on.

CATHERINE LORRAINE: And who explains what the state of the art is? Would that be the investigator?

PAULA KNUDSON: Oh, yeah. I'm not a scientist or an M.D. I can't. I can't. And I'm not an emergency room person. So, yes, the investigator, who is invariably both a scientist and an M.D. and an emergency room person.

CATHERINE LORRAINE: Thank you.

DIANE MALONEY: Just can you comment on how useful you think a discussion of these studies at an open public forum, such as an FDA advisory committee, would be?

PAULA KNUDSON: Oh, I think it would be wonderful. I think IRBs would very much endorse the idea of an--such as the pediatric subcommittee on the ethics, the Pediatric Ethics Subcommittee that Skip Nelson chairs. I think that's just absolutely a marvelous resource for IRBs. We learn from every one of those discussions.

DIANE MALONEY: And would you have concerns with the protocol being discussed in an open forum?

PAULA KNUDSON: I'm sure that sponsors would. There must be some way that protocol can be abbreviated so

that the proprietary information is not disclosed, but the mechanics of what you're doing is disclosed.

CATHERINE LORRAINE: Thank you.

JEFFREY SHUREN: Thank you very much.

PAULA KNUDSON: Thank you for allowing me to speak.

JEFFREY SHUREN: The last speaker today is Lynn White.

LYNN WHITE: Hi. I'm Lynn White. I'm one of the National EMS Research Agenda co-investigators, and Dr. Michael Sayre is our investigator, who's here today in the audience.

The National EMS Research Agenda is a project that was designed to examine EMS research and barriers to its success, and also to recommend strategies to improve the quality and quantity of EMS research, ultimately to improve the care of the patients that we treat out of hospital.

The Research Agenda is supported by the National Association of EMS Physicians, NAEMSP, and also the National Highway Traffic Safety Administration. We were recently awarded an AHRQ grant in support of a conference to discuss

and develop guidelines for IRBs to assist them in the interpretation and application of the exception from informed consent in emergency research rules. And I just wanted to let you all know that our conference will be held on February 7th and 8th, 2007, in Washington, D.C., and it's open and you're all invited, and we hope that several of you will participate. Information on registration isn't yet, but will soon be, on the Web site of NAEMSP, which is www.naemsp.org. And also we have a Research Agenda Web site, and that's www.researchagenda.org.

That's all I have to say. Thank you.

JEFFREY SHUREN: Great. Thank you. Questions from the panel?

All right. Thank you very much. This concludes our hearing. On behalf of the FDA panel, I want to thank all who took the time to attend this public hearing. I want to particularly thank those speakers who took the time to present their thoughts to all in attendance, and I'd like to give all of them a round of applause. (Applause)

Also, a thank you to the FDA panel who came today as well. The agency will be considering the information

that the speakers provided today, along with all other available information, and that includes comments submitted to the docket for this meeting and for the draft guidance.

I will remind folks that the docket is open until November 27th. So, please, if you do have any comments, do send them to the docket. We very appreciate also any data that you may have or any studies. We do look at everything that you send in.

Lastly, I just want to thank everyone again for your attendance, and I wish you a good rest of the day.

Thank you.

(Whereupon, at 3:52 p.m., the proceedings concluded.)