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October 26, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2006D-0331 Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research

Conveyed electronically to: <http://www.fda.gov/dockets/ecomments>

The Association of American Medical Colleges (AAMC) is a nonprofit association that seeks to improve the nation's health by enhancing the effectiveness of academic medicine. It represents all 125 U.S. and 17 Canadian accredited allopathic medical schools, nearly 400 major teaching hospitals and health systems, 96 academic societies, and the nation's 67,000 medical students and 104,000 residents. The AAMC is pleased to comment on this important issue, and is strongly supportive of the overall goal of the proposed guidance, namely to assist those conducting important research to improve the treatment of patients with critical illness and injury, while at the same time protecting the rights of human subjects. With this comment letter, AAMC affirms its support of the comments appended at the end of this letter of two other groups. One is the Society for Academic Emergency Medicine (SAEM), a constituent organization of the AAMC, and the other is the network of investigators supported by NIH/NINDS for Neurological Emergencies Treatment Trials (NETT).

The comments of both of these organizations indicate that the proposed guidance does not address a number of important issues including:

- Patient populations that are not considered in the Final Rule, such as children;
- Definition of “unsatisfactory or unproven” and the need for incremental risk assessment;
- Guidance for out of hospital research;
- Guidance for multi-center trials and the use of central IRBs;
- Defining the purpose and criteria for assessment of community consultation;
- Defining the purpose and criteria for assessment of public notification.

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Food and Drug Administration

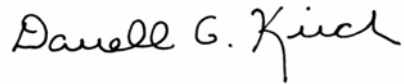
October 26, 2006

Page 2

The NETT investigators have proposed specific guidance language to address some of these areas. While we commend their efforts as thoughtful and well reasoned, we are also mindful of the need for the development of a broad consensus on these issues. Thus, we strongly support the suggestion from SAEM for convening a stakeholders' meeting to revisit the requirements of the Final Rule.

Please contact Howard B. Dickler, M.D. (hdickler@aamc.org; 202-828-0567) of the AAMC staff for questions or clarification of these comments. We thank you again for the opportunity to express our concerns.

Sincerely,

A handwritten signature in black ink that reads "Darrell G. Kirch". The signature is written in a cursive style with a large, prominent "K".

Darrell G. Kirch, M.D.

President

Attachments

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Introduction

The Society for Academic Emergency Medicine (SAEM) is grateful for the opportunity to provide comments from its membership to the FDA related to The Exception from Informed Consent (EFIC) in Emergency Research Circumstances. The Coalition of Acute Resuscitation Researchers (the Coalition) joins SAEM in this presentation, and we include comments from members of the American Academy of Emergency Medicine (AAEM).

In 1994, SAEM took the lead in discussions related to issues of consent in emergency research circumstances. 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 (21CFR 50.24). Since the codification of the Final Rule into Federal Regulations in 1996, SAEM has continued to discuss, educate it members on, and monitor the use of the Final Rule within the emergency research community. In May, 2005, the Society's 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 doing so, we must recognize that the 2006 Guidance document is fashioned around the Final Rule as it currently exists. We strongly believe that a better approach would be to revisit the Final Rule itself, and use existing experience and data to determine whether and where it is meeting its goals, and where its requirements have missed the mark.

The FDA has asked us to consider many questions; we will briefly mention a few general areas to provide focused thoughts related to the issue of EFIC.

Comments on the FDA's questions on;

A. In terms of the **Scientific aspects/ ethics,**

#4. The FDA has asked if there are challenges that have not been explicitly addressed in the regulations in designing scientifically rigorous and ethically sound emergency research and, if so, if these challenges should be addressed now.

We believe 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 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 we would 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 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. Although, in theory, pediatric research can qualify for an EFIC, we believe that better guidance on the application of EFIC or a reconsideration of the Rule's requirements in order to address issues in emergency research in children is paramount.

Resuscitation research also includes studies of varying complexity, across a wide spectrum of 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 to not only 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 or to define as the clinical 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 the 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 use of the Rule. For example, the Institute of Medicine's recent report on the Future of Emergency Care describes a paucity 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 have data that suggests fulfilling the requirements of the Final Rule in the out of hospital setting is inconsistent, even within the same EMS service. We must ask the EMS research community 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 patient populations served?

The translational emphasis of the NIH has led to the development of at least three emergency based research networks (PECARN, -NETT, and ROC sponsored respectively by MCHB, NINDS, and NHLBI). All aim to test new treatments for critical illness or injury. Many studies undertaken by these networks will require research using EFIC. Challenges are always present when trying to successfully and consistently implement a protocol at several sites and we need to determine the unique challenges related to EFIC. For instance, there are variable levels of comfort and experience among IRBs regarding the use of EFIC. The Final Rule vests increased responsibilities and authority into IRBs. The details are complex and to date, IRBs have been given limited guidance and 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 reluctant to allow research using the EFIC, which results in a demographic bias in study enrollment. Should 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 tough questions with very significant 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.

B. Additional human subjects protection

The FDA has asked a series of questions regarding 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, and in fact, much evidence to suggest otherwise. In the decade since the Final Rule was established, less than a dozen studies examining the methodology of community consultation have been undertaken and published. These studies have documented the ambiguity inherent in conducting community consultation and 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. Data from the Public Access Defibrillation trial suggest that even members of focus groups with multiple educational sessions, do not generally understand the actual study goals and protocol. The Final Rule asks for community consultation but does not require a measure of its effectiveness. How, then, do we make sure the community understands? To our knowledge there is no formal reporting of how community consultation has altered

protocols using EFIC and very little information about how IRBs utilize the information provided. 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 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 is to be conducted. Studies that have documented this process have shown that few people attend public meetings and those who do are likely to be non-representative of the at risk community being studied. For example, we conducted 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 the community is providing feedback and does it reflect the true concerns of the targeted study population? How do we know that we have heard their potential concerns, since we do not 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 this purpose is still meaningful

We do not believe it will ever be possible to determine if community consultation provides adequate patient safeguards against research risks since there are no measures of its effectiveness and no possible way to quantify it. Therefore, instead of asking if CC provides adequate patient safeguards, the better question is, "How can we better protect patients?"

Public notification and disclosure are other safeguards built into the Final Rule. Disclosure of a full research protocol or certain scientific information to the public may cause concerns similar to those outlined above. However, the intent is different; it is a disclosure and not a discussion. If we include protocols or specific scientific information in the public notification, how can we be sure the public understands? Does the public really need to know all of these details? Even more basic, can we be sure that this information actually reaches the public, as the process was intended? As an example, we interviewed patients in ED waiting rooms in three large cities after a very aggressive and widespread public notification campaign had been conducted regarding the existence of a study using EFIC. Less than 5 % of individuals surveyed at any of the sites actually knew of the study.

Conclusion

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 a patient protective manner remains unknown.

We appreciate the FDA's willingness to listen to our comments and hope this information will prove 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 has not effectively and meaningfully provided the safeguards for vulnerable patients as intended. 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, and 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 about 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.

The NIH/NINDS Neurological Emergencies Treatment Trials (NETT) investigators

We wish to commend the FDA on drafting this new guidance statement regarding the regulations found at 50.24. As recognized in the introduction to the guidance, much effort and thought has gone into the consideration and implementation of these rules in the 10 years since they were adopted. In one sense, it is appropriate that use of these regulations has been quite limited, since trials should use exception to consent only when other options are not possible and when sufficient resources are available to ensure that the trial can achieve the conditions and safeguards required under the regulations. Trials that use emergency exception without adequate protection of human subjects cannot be allowed. On the other hand, it is problematic if potentially life-saving research is inhibited by confusion regarding the regulations, or by the interpretation of rules in ways that dissuade research without actually protecting subjects.

The timing of this new guidance is 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 National Institutes of Health (NIH) has recently funded three new clinical research networks to address these problems. It is expected that all three networks will conduct some trials that can only be accomplished with emergency exception to informed consent. We are here to represent the Neurological Emergencies Treatment Trials (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 hemorrhages, infections such as meningitis and encephalitis, and other conditions that present in the emergency department. The other two networks are the Resuscitation Outcomes Consortium (ROC), led by the NHLBI and cooperatively funded to study treatments for cardiac arrest and traumatic hemorrhagic shock, and the Pediatric Emergency Care Applied Research Network (PECARN), led by the MHCB and cooperatively funded with the NICHD to study pediatric emergency care.

The purpose of the new guidance document is to help potential subjects, investigators, institutional review boards, and regulators reach a common understanding of the regulations, an understanding that both protects subjects and permits critical advances in emergency medical care. The posted draft guidance goes a long way to achieving this purpose. In a number of areas in which the regulations are quite vague, the guidance provides specific examples. To its credit, it is also very clear in the guidance that these are meant to be merely examples and that the specific circumstances of any proposal may vary. We are 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 this 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 is 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 will address five specific concerns, and in each area we will propose both specific recommendations and an underlying ethical rationale that we feel may represent the regulatory intent of the relevant provision. The areas that we wish to address include:

1. The purpose of public notification
2. The purpose of community consultation
3. The potential use of a central IRB
4. The definition of “unsatisfactory or unproven”
5. The use of active controls

The purpose of public notification

Public notification as a requirement in research conducted with exception to informed consent is likely to have multiple purposes. The hierarchy of these purposes is easy to get wrong because of dissimilarity to the most common analogies. That is, public notification is likely to look just like other forms of advertising or public service announcement, but it has a different primary purpose. The primary purpose of public notification is different than that of Macy’s advertising a sale, or of 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 are trying to change the behavior of the ad’s target, the potential shopper. They want that person to come to Macy’s when they would not 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 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 Macy’s ad and the purpose of public notification has important implications. Let us consider two of these. (1) The former requires a receptive audience. The Macy’s ad presumes that there are shoppers interested in buying chino’s and are looking for a place to do so, and are unlikely to be successful otherwise. The latter only requires the potential for (or 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. (2) Consequently, the success of a Macy’s ad and a 50.24 public notification must 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 a 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, i.e., at dissuading the investigator from proposing something unacceptable or controversial, the less likely the public is to notice or react to the notification.

Guidance: (part VIII.B, page 16) the primary purpose of public notification is to ensure transparency about the research being conducted. Adequacy of public notification efforts should be assessed based on the potential size of the audience, the openness and readability of the content of the message, and the rigor of the communication effort, and is not best assessed by surveying the audience.

The purpose of community consultation

Community consultation is another important aspect of the regulations at 50.24, 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 is 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. Such feedback may be used to help investigators clarify or modify study materials or procedures, or to inform IRB decisions on final approval of a study. The proposed guidance is helpful in suggesting some possible details regarding the mechanics of community consultation, i.e., organization of meetings, who might attend, how the results are fed back to the IRB, etc., and community is defined both geographically and by predilection to the conditions of study enrollment.

Conspicuously absent is any description of the specific kinds of feedback that should be solicited from the community consultation process. To determine the kinds of feedback desired it again is important to know the intent of the process. Why require community consultation, and what is to be gained by this process? Clearly there is an intuitive value to community consultation, but a more precise identification of its intent is not obvious. At first blush one could argue that the intent is to gather any and all feedback. Certainly, if one is going to do community consultation it is reasonable to design the process to collect any and all feedback, but that cannot be the intent. For example, if one intended to get feedback on the scientific validity of the methodology, one would not create a community consultation process to do so. It would be an ineffective or at least profoundly inefficient way of obtaining scientific review.

The intent of community consultation may also be misconstrued by analogy to circumstances that look somewhat similar but are not ethically comparable. In this case, the mistaken analogy is to the informed consent process used with individuals who are offered enrollment in a clinical trial. Community consultation is not a “community consent” process. Why not? The informed consent process is an application of personal autonomy. The most salient characteristic is that one is deciding for one’s self what will happen to one’s self. Although the informed consent process 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, etc), these are all outweighed by the value placed on patients being the deliberative decision makers because they will personally benefit or suffer the consequences. When patients cannot choose for themselves, a surrogate decision making process must be used; most often we ask someone close to the patient what the patient would have wanted if they were able to decide. We choose these surrogates based on their special personal knowledge of the patient’s desires. A community discussing issues in abstract, by contrast,

cannot have personal knowledge of the desires of an anonymous future subject, and cannot represent the personal autonomy of subjects, therefore the community cannot provide consent. In other words, asking the community to provide consent maintains all the weaknesses of the personal informed consent process, without having the one saving grace (personal autonomy) that makes it worthwhile. It is the worst of both worlds.

On the other hand, the community can be extremely valuable in sharing the values and context that are prevalent in its members. It has 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 shared lore or mythology) may be useful in informing surrogate decision making in emergency research with exception to informed consent. This emotional and cultural context should be the primary feedback sought during community consultation. It is this information that is difficult for investigators and regulators to obtain in other manners. An element of the research taken for granted by investigators may resonate very strongly in a potential subject's community because of a shared emotional memory. In the recent PolyHeme trial controversy, for example, it has been argued that the fear of being deprived the life saving properties of blood transfusion was hyperacute in African-American communities because this had been a prior common manifestation of bigotry in the US. It is easy to imagine that investigators may not have been thinking of this historical context when planning the trial. Ideally, community consultation should have alerted investigators to the special sensitivity of this concern, which they could then address in a number of ways. A key response might simply be the honest acknowledgement 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 transfusion of hemoglobin, and the protocol could have been revised to state this more clearly. It is likely that most community objections can be addressed by acknowledgement and validation, by supplemental explanation and clarification, or by revisions to the protocol. When they cannot, investigators or regulators should decide not to conduct the trial in that community (or at all).

Guidance: (part VIII.A, page13) the primary purpose of community consultation is to provide a discussion in which investigators and regulators can learn the relevant values and narratives that underlie a community's emotional and cultural response to the proposal. Community consultation is not a consent process; the community is not asked to decide on the proposal. Responses to community consultation may include honest acknowledgement and validation of the expressed feelings and opinions, supplemental explanation and clarification of the protocol, or appropriate revisions to the protocol. In the absence of concerns, no changes are required. Concerns and responses will inform investigators and regulators in their decisions to pursue or approve the proposal.

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 from many local institutional review boards. As a result there is concern that application of the rules may be inconsistent from one institution to

another, and 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.

The proposed guidance already requires investigators in multicenter trials to inform every participating IRB if the protocol is rejected by any IRB review. This unusual requirement may be helpful in reducing variability, but is limited because a proposal may be turned down in any given locale for a variety of reasons, and because there is no well established format to ensure that the reasoning of an IRB is documented or shared with the other boards. Furthermore, this requirement does not appear to apply if an application is withdrawn from review. Centralized review of the key provisions of a proposed trial by a board capable of developing and maintaining expertise relevant to exception to informed consent would be more effective at improving review quality and decreasing variability.

Trials that have successfully used the regulations include those conducted in a single locale (e.g. the Prehospital Treatment of Status Epilepticus trial, PHTSE) and those conducted at sites across the country (e.g. the Public Access Defibrillation trial, PAD). In the near future it is likely that multicenter trials will predominate because more and more federally funded trials are likely to require the use of 50.24 in the next several years. At least three multi-center clinical research networks have recently been funded to study emergency therapies in different types of critically ill and injured patients. The Resuscitation Outcomes Consortium (funded by several agencies and led by the NHLBI) and the Neurological Emergency Treatment Trials network (funded by NINDS) are developing and will continue to develop studies that cannot be completed without exception to consent for emergency research. The Pediatric Emergency Care Applied Research Network (funded by the HRSA/MCHB and the NICHD) is also preparing trials requiring emergency exception. This increasing number of studies with exception requiring review poses both challenges and opportunity to our national 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 Armitage Report (the Report of the National Cancer Institute (NCI) Clinical Trials Program Review Group) in 1997 recognized that participants in large federally funded oncology trials were subject to "inconsistency and potential inequities in the quality of Institutional Review Boards (IRBs) across the United States". In the context of clinical trials conducted by large multi-center research groups, the report recommended that a national streamlined IRB process would "assure that all patients are treated equally, and are provided 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 a trial conducted around the country had the benefit of an equal, expert, and high quality IRB review of the trial proposal. This solution has similar potential benefits to patients enrolled in large multi-center trials using emergency exception.

The NCI, working with the Office for Human Research Protections (OHRP), created the Central Institutional Review Board (CIRB) initiative in response to the concerns for human subjects expressed

in the Armitage report. The NCI Adult CIRB has been meeting twice monthly and reviewing clinical trials since January 2001. The Adult Board currently reviews all Phase 3 Cooperative Group trials from all 9 large NCI funded clinical trial networks, as well as any other protocols opened in the Cancer Trials Support Unit. The Pediatric CIRB was constituted in June 2004 and began meeting in November 2004. It reviews all NCI-approved Children's' Oncology Group Phase 2, 3, and Pilot protocols. Acceptance of the NCI CIRB has been excellent. Currently over four hundred and fifty institutions in over 40 states are participating in the Initiative. Participants include many of the country's leading research universities, as well as many smaller community hospitals. Here is a synopsis of how the NCI CIRB process works:

1. The Adult or Pediatric CIRB receives a completed application, protocol, informed consent form and related materials from the Clinical Trial Cooperative Group.
2. The full Board conducts initial review and, as appropriate, approves, disapproves, or returns the protocol to the investigators for amendment.
3. After the protocol is activated by the Cooperative Group, all review documents are posted on the website for access by participating institutions.
4. A site investigator at a participating institution wishes to enroll subjects in a CIRB-approved protocol. Either the investigator or local IRB downloads the application packet for facilitated review.
5. The local IRB chair/subcommittee conducts a facilitated review, concentrating on local context issues.
6. The local IRB notifies the CIRB Administrative Office of facilitated review acceptance via the website.
7. The CIRB becomes the IRB of Record for this protocol and is responsible for continuing review as well as review of subsequent amendments and serious adverse events (SAE) as notified by the Group.
8. Local IRB is responsible for review of local SAEs and oversight of local conduct of the study.

The CIRB allows a concentration of expertise, so that reviewers (both scientific and ethical) on the board are already familiar with the background, science, and relevant concerns involved with type of research being proposed. Community members of the board that may not have focused expertise at the outset gain familiarity with the relevant concepts and regulations more quickly through concentrated experience.

The availability of expertise is especially valuable to local IRB of smaller institutions that may not have sufficient resources to provide an adequate review from within their own ranks, and whom might otherwise have to resort to a commercial IRB or simply be unable to review the proposal at all.

CIRB review saves thousands of hours of redundant local IRB review, and allows the local IRB to concentrate their efforts on important local context issues. Centralized oversight ensures that these efficiencies continue throughout the life of the trial.

A centralized IRB process simplifies the regulatory oversight required of the FDA and the OHRP. Rather than auditing and enforcing the relevant regulations at hundreds of sites across the country, regulators can more easily observe and influence the application of the regulations at section 50.24 through a single IRB whose processes serve the others.

Successful organization of the ER-CIRB requires early involvement and buy-in by the FDA which has had limited involvement with the NCI-CIRB, and by the OHRP which has worked closely with the development of the NCI-CIRB and been very satisfied.

An Emergency Research CIRB is needed to provide consistent, equitable, expert protection to the human subjects participating in emergency research conducted in the newly funded NIH emergency research networks. It also enhances the efficiency of the clinical research enterprise, and makes regulation and oversight easier and more effective.

The proposed guidance specifically allows for the use of a CIRB, but it has been construed 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, centralization of the primary application would free up substantial resources of the local IRB, allowing for better local review. The guidance should therefore also be clearly compatible with efforts at NIH and elsewhere to improve the protection of human subjects through centralized review providing that (1) participation is voluntary on the parts of local IRB, and that (2) the process is approved by the OHRP and the FDA.

***Guidance:** (part IV, page 8. Language from the proposed guidance is in italics, our recommended additions are in blue without italics) FDA anticipates that emergency research usually will be performed at an institution with an IRB that has the responsibility for reviewing the study at that institution. Independent IRBs may also review emergency research studies involving an exception from the informed consent requirements. In federally sponsored multicenter trials a federally funded central IRB may be used to work cooperatively with local IRBs to enhance availability of expertise, share resources, and decrease variability of review. The IRBs need to be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice and therefore IRBs need to include persons knowledgeable in these areas (21 CFR 56.107). IRBs that review research under this rule need to be knowledgeable about local conditions in order to evaluate the plans for community consultation and public disclosure. This condition can be met by local IRB reviewing local context issues in cooperation with a central IRB. Institutional responsibility for these studies should not be delegated to another IRB unless the local IRB and the administration of the institution agree. Participation with a central*

IRB must be voluntary. *Any agreement to allow review by a non-local IRB should be in writing. 61 Fed. Reg. at 51504 (Comment #18). Copies of any agreements should be provided to all parties involved in conducting the research (e.g., the institution, local IRB, independent or central IRB, clinical investigator(s)).*

The definition of “unsatisfactory or unproven”

Interpretation of 21 CFR 50.24 has sometimes been difficult, in part, because of relatively little guidance in defining the regulation’s terms. Exception to consent is only permitted, for example, when the available treatments for the life-threatening condition being investigated “are unproven or unsatisfactory,” but how does one define unsatisfactory in this context? Although this was identified as a question to be discussed in the notice of this hearing, the proposed guidance does not attempt to define these terms. We propose an operational consensus definition formed during a conference on “Ethical Conduct of Resuscitation Research” convened in New York City in May 2005. The conference included physicians, regulators, administrators, and ethicists. This group 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 this regulation means to help.

Divining the intent and ethical basis of the regulation provides a more robust and useful definition of “unsatisfactory”. The consensus opinion was that “existing therapies should be considered ‘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” (Watters 2005).

It was felt the regulatory intent and definition of “unsatisfactory” is to exclude studies where no improvements in outcome are proposed, i.e., comparisons of one satisfactory treatment versus another satisfactory treatment. In defining “unsatisfactory” the consensus 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 existing therapy. The research must have the prospect of benefiting patients and society” (Watters 2005). 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.

Guidance: *(Appendix A) Unsatisfactory (definition). Existing therapies should be considered ‘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.*

Study design and the use of active controls

Study design must be carefully considered in trials conducted 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 further clarification. The guidance points out several possible designs. The most common design will compare standard therapy plus placebo to standard therapy plus a test treatment. The guidance also acknowledges rare situations where an element of standard therapy (A) is unproven or unsatisfactory and allows comparison of standard therapy to standard therapy minus A. A third design, one with active controls, is implied by the first two, but is not explicitly described in the guidance. Active control designs are also likely to be common and the guidance should comment on when they are permissible. When an element of standard therapy (A) is unproven or unsatisfactory, and a proposed test treatment (B) (with potential for direct benefit to the subject) is mutually exclusive of A, comparison of standard therapy with B instead of A to standard therapy including A is permissible. This is only permissible if the therapies are mutually exclusive. Mutually exclusive therapies would include situations in which the test therapy is a different dose of the same medication, a more effective therapy sharing the same action, or an alternative version of the same therapy but with fewer serious adverse events. For example, in studies of hemorrhagic shock it may be permissible to compare fresh whole blood to packed red blood cells. In studies of cardiac arrest, it may be permissible to compare fast ventilation to slower ventilation, to compare epinephrine to vasopressin, or to compare bretylium to amiodarone. In studies of status epilepticus it may be permissible to compare a potentially faster acting, longer acting, or less sedating benzodiazepine to a standard benzodiazepine.

***Guidance:** (part II, page 5) Active control studies comparing an unsatisfactory element of standard treatment to an alternative test treatment are also permissible, providing that the test treatment: (1) offers the prospect of benefit to subjects by being potentially more effective or less risky, and (2) is mutually exclusive of the standard treatment. All other elements of standard treatment (if any) would be given to all subjects.*

We appreciate the opportunity to share these concerns and recommendations with the FDA. The mission of our new emergency research clinical trials networks (NETT, ROC, and PECARN), and of the NIH, is to find better ways to reduce the suffering and premature deaths of people with medical emergencies. The path to successfully completing that mission in a manner that is safe and respectful of human research subjects relies on the provisions of exception to consent for emergency research and on partnership with the FDA and the OHRP.

Thank you.

