

Response to FDA Draft Guidance Statement on Research into the Treatment of Life-threatening Emergency Conditions using Exception to Informed Consent

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

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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) and other agencies have 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 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 meningitis and encephalitis, and other conditions that present in the emergency department. We are here today with representatives of the other two emergency networks, 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 MHCBC and cooperatively funded with the NICHD to study pediatric emergency care. We have worked together to provide coordinated commentary and suggestions regarding the proposed guidance. We support the statements of our colleagues and will avoid duplicating their important points in this presentation.

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

These comments contained here will variously address questions 2, 9, 12, 20, and 21 in Section V of the Notice of Public Hearing [Docket No. 2006D-0331]. For each comment, we have also recommended specific language for a revised guidance document.

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, page16) 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 accessibility 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, *Acad Emerg Med* 2005;12:1040-1044).

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.