

COMMENTS

**GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS, AND CLINICAL
INVESTIGATORS, AND SPONSORS**

**DRAFT GUIDANCE EXCEPTIONS FROM INFORMED CONSENT
REQUIREMENTS FOR EMERGENCY RESEARCH**

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Submitted by:

Leonard H. Glantz, JD
Professor of Health Law, Bioethics
and Human Rights
Boston University School of Public Health
715 Albany Street
Boston, MA 02118
(617) 638-4644
lglantz@bu.edu

Matthew Baratta
Cynthia Glennon
Sonya Khan
Master of Public Health Candidates

NOTE: These comments are submitted by the authors in their personal capacities and do not represent the official views of Boston University or the School

Introduction

Research with human subjects without informed consent is presumed to be unethical. Every ethical code, law and practice starts from this point. Indeed, the foundational document for most of these codes and laws, the Nuremberg Code, starts with the proposition that “the voluntary consent of the human subject is absolutely essential.” The purpose of making informed consent a precondition to using a human being as a research subject is to protect both the rights and the dignity of the person. Since the goal of research is designed to develop new knowledge instead of, or in addition to, benefiting the particular research subject the researchers are asking the subjects to provide them with a gift. The gift is the use of their bodies as a research tool for the benefit of a larger community. Without the informed consent of the subject, there can be no gift. Rather it would be taking something from the subject without their knowledge or consent. Indeed, research without consent treats a human being simply as a means to an end rather than as an end in and of themselves.

Since the promulgation of the Nuremberg Code, more recent codes have dealt with difficult questions regarding the ethics of exceptions to the informed consent requirement. For example, parents have been deemed to be suitable surrogates in regard to giving consent to research using their children. This is particularly true when the research holds out the prospect of direct benefit to the child-subject. In circumstances in which there are no direct benefits to the child-subject but there exists the possibility of harm, the issue of the appropriateness of surrogate consent has been subjected to ongoing debate. Since the emergency regulations only pertain to research which holds out the prospect of direct benefit to the subject, this is not a consideration in this instance.

Surrogate consent is based on the notion that someone motivated to protect the rights and welfare of the nonconsenting subject is acting on her or his behalf. But this is not the case with emergency research. Emergency research raises some of the most difficult ethical and legal issues in regard to its permissibility. It is research with *no* consent, personal or surrogate. On its face, this would appear to be a clear violation of the Nuremberg code, and other ethical codes as well as some case law.

21 CFR 50.24 addresses this most serious ethical issue by setting forth strict conditions that would permit research with human subjects who are *dying*, for whom there is *no* good treatment and the research holds out the prospect of *saving the life* of the subject. It is permissible only because desperate situations permit desperate measures – measures that would be unethical and impermissible in all other circumstances. In a very real sense, emergency research is a combination of innovative therapy and research. In order for such research to be acceptable animal and prior human studies must show that there is a bona-fide prospect of life-saving benefit.

The FDA Guidance should highlight the extraordinary nature of this class of research, and the fact that in the absence of dire need of an intervention to save a life that such research would be unethical and would not be authorized by the FDA. Our comments are

designed to help the FDA ensure that such research is only conducted in such extraordinary circumstances and only with full transparency.

Page 3 - Trials with morbidity endpoint

The bottom of page 3 addresses trials that have morbidity endpoints rather than mortality endpoints. This is quite troubling. 21 CFR 50.24(a)(1) requires that human subjects are in a "life threatening situation, available treatments are unproven or unsatisfactory" and the research is "necessary to determine the safety and effectiveness of particular interventions." The definition of "life-threatening" on page 25 of the Draft guidelines refers to diseases or conditions where the "likelihood of death is high unless the course of the disease or condition is interrupted. 21 CFR 50.24 applies only to life-threatening emergency situations."

It is quite clear from the regulations and from the definition in the Draft Guidance that this class of research is permissible *only* when the "likelihood of death is high" unless an intervention with the prospect of direct benefit occurs. Given this, the 21 CFR 50.24 as currently written would not permit research with nonconsenting subjects whose primary end point is morbidity rather than mortality. If reduced mortality is not the primary endpoint, there is no reason to restrict such research to subjects who are in life-threatening emergency situations. Similarly, the term "prospect of direct benefit" can only be interpreted to mean an amelioration or elimination of the life-threatening situation of the subject. It may well be the case that research on *unconscious* individuals may provide valuable information that would reduce morbidity. But the current emergency regulation does not authorize research with that subject population. Adding this additional population to the class upon whom research without consent may be conducted would require a new rule-making procedure.

Page 5 - Use of Placebos

21 CFR 50.24 (a) (1) authorizes the conduct of placebo controlled studies with non-consenting human subjects if placebo controlled studies are necessary to "determine the safety and effectiveness of particular interventions." The Draft Guidance state placebos would be administered in addition to standard of care in "virtually all cases." Justifiable studies where standard care would not be provided are only those in which the research objective is to "determine if some aspect of standard treatment is in fact useful."

The Draft Guidance should make it clear that the subjects in the placebo arm of the study still must fit within the general restrictions of 21 CFR 50.24. That is, for the placebo group from whom standard care or an aspect of standard care will be withheld, the prospect for direct benefit must still be present. When standard care, or an aspect thereof, is withheld there must not be increased risk to the patient, but rather the prospect for direct benefit as required in 21 CFR 50.24 (3).

In order for there to be a prospect of direct benefit from the administration of a placebo in lieu of standard care, the standard care must reasonably be hypothesized to be harmful, and therefore withholding such care would provide the prospect of direct benefit by decreasing the risks of the standard intervention. Excluding the placebo group from the requirement that there be a prospect for direct benefit, which is a condition of enrollment for all other subjects of emergency research, results in using these subjects solely as a means to an end, and removes the study from the special moral status assigned to emergency research

The Guidance should include an additional condition for the use of placebos with this population - all attempts at obtaining the same information without the use of such a placebo must be exhausted. An attempt should be made to gather the necessary information through a review of cases in which standard care was refused either by the patient or through a proxy, or through the use of subjects that have the capacity to consent. Should this be impossible, the use of a placebo group that cannot offer consent that meets the above criteria could only be employed when the information provided by the placebo group is absolutely necessary, not just desirable, and of a nature that is impossible to derive from any other means.

Page 7 – IRB requirements

The Guidance should clarify what it means for an intervention to be “unsatisfactory or unproven.” It should be made clear that the fact that the sponsor and investigators believe the research intervention is better than standard care does not make standard care “unsatisfactory.” If someone is in a life-threatening situation, and the current therapy offers a proven 90% chance of survival, the fact that a proposed therapy might have an unproven 95% chance of survival, does not make the 90% chance of survival with standard therapy “unsatisfactory” by any stretch of the imagination. Given the fact that the precondition to, and ethical justification for enrolling a nonconsenting subject into this class of *emergency* research is based on the life-threatening situation of the subject, effective life-saving treatments should not be withheld.

Page 7 of the Draft Guidance states that IRBs must ensure that there are appropriate procedures in place to inform subjects or their legally authorized representative of the right to discontinue participation in the research. While this is entirely appropriate, it is useful to note that in the circumstance of emergency research this right will unlikely be enforceable in any important way. Once an intervention is made on an unconscious subject, such as the use of a device or the administration of a new drug, such interventions often cannot be undone. The reason why this should be explicitly stated is that IRBs should not rely on the general ability of subjects to discontinue participation in research when considering the appropriateness of emergency research

The second bullet point on page 7 of the Draft Guidance states "the IRB reviews these materials and determines whether the criteria are satisfied and the research may be

conducted under 21 CFR 50.24, pending consideration of the input received from community consultation activities.” This statement seems to confuse the IRB’s obligation with the role of community consultation. Whether the specific criteria of 21 CFR 50.24 are satisfied is a determination that can be made solely by the IRB, and its determinations can not be informed by community consultation. For example, community consultation cannot inform the IRB whether or not the subjects’ conditions put them in a life threatening situation; whether participation in the research provides the prospect of direct benefit to the subjects; whether appropriate animal and other preclinical studies have been conducted; whether current treatments are unproven or unsatisfactory; and so forth. These are technical and scientific determinations that cannot be informed by the general community. Such findings are solely and entirely the responsibility of the IRB, and this should be made absolutely clear in the Guidance document.

Page 8- Independent IRBs

Independent IRBs should *not* be permitted to be used by institutions that propose to conduct research without consent. There are two reasons for this. First, the regulations not only require community consultation, but clearly imply that sensitivity to community concerns is an important aspect to approving such research. A local IRB is much more apt to have sensitivity and knowledge of local concerns than an IRB thousands of miles away.

Second, as we noted in the introduction to these comments, research without consent is the most ethically questionable category of research that can be performed on human subjects. Only institutions that demonstrate the highest level of concern for the protection of the rights and welfare of human subjects should be permitted to conduct this class of research. Lack of an internal IRB would strongly indicate that the institution does not meet this high standard.

Page 9- Documentation

IRBs should be required to make a separate finding regarding each of the regulatory conditions that must be met to approve emergency research without consent. Furthermore, a separate vote should be taken on each finding. The IRB should also be required to specify the information upon which it relied to make the required findings. For example, it should make a specific finding of what constitutes a “life-threatening situation” in the proposed research, and a justification for its conclusion that “available treatments are unproven or unsatisfactory.” To be clear, the IRB should be required to justify and document its conclusion that standard treatments are unproven or unsatisfactory, that there is a prospect of direct benefit from the research intervention and for all of the other required findings.

Page 9- V. Physician Concurrence

The Draft Guidance does not make clear with what or who a licensed physician is supposed to concur. Indeed, it does not require that a concurring physician have any expertise in providing emergency or life saving care. Does the Draft Guidance mean that one physician must be in the majority of the IRB that approves such research? Does the Draft Guidance require a sole physician to make independent findings of each of the criteria required to approve such research? The Guidance seems to give a concurring physician more authority than a dissenting physician. What if one physician concurs and two dissent? If the physician on the IRB does not concur, may the IRB contract with another physician who would concur? This requirement needs substantial clarification.

The basic issue is whether this requirement adds an additional layer of real protection, or only apparent protection since finding some physician who would concur with a sponsor, investigator or IRB would not be particularly difficult.

Should the FDA retain this requirement the IRB should document who the designated “concurring physician” is and how she or he was chosen to serve in this capacity.

Page 12- VIII Community Consultation and Public Disclosure

We agree with the Draft Guidance that community consultation and disclosure should be as meaningful as possible. However, it is important to recognize that the community consultation is likely to reach a very tiny minority of individuals in the community. While efforts can and should be made to increase attendance at these community consultations, it must be recognized that this is largely an ineffective way of making it widely known that research without consent is going on in the community. Experience indicates that the number of people who attend such community events is very small compared to the number of people who might be affected by the research. In terms of informing the community that such research is being proposed, detailed and well executed disclosures are more likely to reach larger numbers of potentially affected individuals than community consultation. Indeed, the most effective way of informing community members that they may find themselves being subjects of research without their consent would be to mail each household in the area from which potential subjects will be drawn a notice of this fact and information about how to obtain further details.

Consultation and public disclosure should largely serve the same purpose. The difference between community consultation and public disclosure is based on the nature of the feedback the public can provide and not the nature of the information that needs to be disclosed. Community consultation is supposed to provide a forum for the opportunity for immediate feedback whereas disclosure does not focus on immediate feedback.

It is important not to refer to people who attend or sponsor community consultation meetings as “representatives” of the community. Individuals who attend such meetings

are neither implicit nor explicit “representatives” of other individuals in the community. They are simply individuals who happen to be present at the meeting to gather information for themselves and not for others. To refer to these individuals as “representatives” gives them an appearance of authority or surrogacy that they do not have.

Every member of the community should have access to the same amount and kind of information whether or not they attend community meetings, or are computer savvy or not. Disclosures of information should be available in both paper and electronic form. The paper form should be available at the community consultation meetings as well as available at designated public facilities such as town/city halls, public libraries, post offices, public school libraries and other public establishments. Special care should be taken to ensure that disclosures reach minority populations. For example, if a particular community has a large homeless population, information about the research should be posted at homeless shelters. Materials must be available that are accessible to non-English speaking populations that reside in the community from which research subjects will be drawn. In general, careful and complete steps must be taken to ensure that the disclosure of information pertaining to the research study reaches the largest number of potential subjects.

Complete information about the research should be available on the internet. Specifically, a clearly marked link should appear on the sponsoring company’s welcome/homepage that makes a clear reference to a disclosure of information pertaining to all emergency research it is conducting. The link should go to a page that provides information by community.

Every hospital or other healthcare institution conducting or planning to conduct emergency research must have a link on its welcome/homepage stating that emergency research is being proposed or being conducted at the institution (depending on where in the process of this institution is) with a link to all relevant information necessary for full disclosure.

Suggested mandatory disclosures

The disclosure should begin with a **description of how non-emergency research is ordinarily conducted**, including the philosophy and practice of informed consent and the subject’s right to withdraw at any point. It should be explained that emergency research is an exception to this rule, and that it is generally considered unethical not to get consent of a human subject although there are exceptions to this general requirement. It must be stressed that this is a very unusual circumstance.

The **complete consent form must be available** at all community consultations and online. This will require no additional effort on the part of the sponsor or the IRB as such a form must be created for use by legally authorized representatives if they are available.

The FDA requirements for authorizing emergency research without consent must be disclosed. There should be an **explanation of how, in the opinion of the institution, the emergency research it proposes to conduct meets each of the FDA requirements.**

There should be a disclosure of **arguments of opponents of such research** so community members and other interested parties are made aware of the positive and negative aspects of the research being conducted. The disclosure of the ethical consequences of emergency research without consent is as important as disclosure of the risks of bodily harm that are ordinarily disclosed. Community members may not be aware of the important ethical issues related to not obtaining informed consent from research subjects and this must be communicated to the community.

A description of the standard treatment, if any, must be disclosed and the reasons why the standard treatment is considered "unproven or unsatisfactory" to save the lives of people in a life-threatening condition. There must be full disclosure of what is known about the standard treatment and why it is regularly used. There must be **an explanation of the experimental treatment** or procedure or product and why this experimental procedure has the prospect (not just potential or hope) of being life-saving.

The full research protocol must be made available in paper form at community consultations and online at the sponsors and research institutions websites. **A company should not be permitted to withhold any information** because it believes the information constitutes trade secrets. There must be complete transparency when bypassing important protections of human subjects. If the research is important enough for subjects rights to be vitiated it is important enough for these less important commercial rights to be vitiated.

An explanation of placebo use, if applicable, must be made to the community. What a placebo is, why it must be used, and how the use of a placebo may affect the safety of the subjects must be disclosed.

In addition to a basic discussion of risks involved in the research, the disclosure must thoroughly address the **consequences of the research hypothesis being wrong** in regard to the effectiveness of the research intervention. There must be a disclosure of the safeguards that are in place to reduce the impact of this possibility, and the extent of morbidity or mortality that may result if the procedure or product does not work as hypothesized. The consequences of ineffectiveness must be clearly communicated. If the failure of the research intervention would prolong or increase pain or suffering, this must be disclosed.

Finally **the financial interests of the parties involved in the research must be disclosed.** It must be disclosed whether the sponsor is a for-profit, not-for-profit, or governmental entity. The financial interests of the sponsor, individual investigators, and research institutions must also be fully described. This includes the impact of both positive and negative findings on the financial well-being of the sponsors, investigators and research institutions

Page 14 – Methods for identifying individuals who do not wish to be a research subject

The Draft Guidance states that the community consultation must "provide information about ways in which individuals wishing to be excluded may indicate a preference." A recent sponsor of nonconsensual emergency research made a plastic bracelet available to anyone in the community who wished to manifest their desire not to be research subject. Not surprisingly, few people took advantage of this and there is evidence that very few people were even aware of this possibility. While we think very few people would actually take advantage of any method of manifesting refusal to be research subject, there are methods for facilitating this process for those in the community who would wish to manifest their refusal. For example it would be helpful to be able print a wallet-sized document from the company's web-site stating that an individual refuses his or her consent to be enrolled in the trial. Such documents could also be printed from the health-care facilities' websites. These documents should be made available at all of the public disclosure sites as well such as libraries, towns/city halls and other sites mentioned earlier as distributors of a disclosure documents. Such documents could also be printed in newspapers as well as local newspaper website when public disclosures are made in that media.

Pages 19-20 Public Disclosure After the Study is completed

We agree with the Draft Guidance that there are two distinct audiences that should be made aware of the projects findings. Findings should be presented in traditional scientific publications and at professional conferences for the benefit of practitioners and researchers. The more challenging and untraditional aspect of public disclosure is the task of making understandable disclosures to the lay public, including research subjects or their legally authorized representatives. Since researchers and sponsors will generally not be familiar with, or adept at, presenting outcomes data to a lay audience the FDA Guidance should contain specific elements of what must be disclosed.

Suggested mandatory disclosures

It is critical that both the positive and negative research outcomes be disclosed to the general public, and directly to the subjects and families of subjects who participated in the research. Positive and negative results should be available regardless of whether these results are published in scientific or medical journals. *All* results must be available so the public may learn about the specific and general implications of performing emergency research in their community, and whether to support similar future research.

Results that do not verify the sponsor's hypothesis and the occurrence of all expected and unexpected adverse events and positive findings must be made available both to the scientific community and the public. There should be a specific assessment of how the **research compared to the standard of care**. Raw numbers should be available to the public as well as comparative numbers and percentages. For example if 99 patients out

of 100 die when treated with standard care and 98 out of a hundred subjects die with the investigational intervention, it is not sufficient to inform the community that twice as many people survive with the investigational intervention. While technically accurate this presentation of the data would be misleading to the general public.

At a minimum the following elements need to be disclosed in documents that are written at a sixth grade level of understanding. In addition the sponsor investigator or institution may use other forms of media such as audio and video presentations as long as they are understandable at the sixth grade level.

- A statement that informed consent was not obtained from the study subjects, the subjects were not volunteers, and that this is very unusual for medical research with human subjects
- Number of subjects enrolled who did not give informed consent and the number of people in the study who were able to provide informed consent
- The purpose and hypothesis of the study, and reasons why the study was conducted in the emergency setting without the informed consent of subjects
- An overview of the public disclosures and community consultation that occurred before the study began
- The ethnic, racial, linguistic and gender makeup of the subjects
- Why the research was conducted in a particular community
- How research subjects were selected
- Results, both positive and negative, in clear and understandable terms. As applicable, results should include:
 - Whether or not the results support the hypothesis of the research
 - Whether or not the results confirmed or deviated from results of prior animal studies that used the method, device, or investigational agent
 - Whether or not the investigational method, device, or agent is safe and effective
 - The availability of the investigational method once it is approved
- Adverse events, frequency, and the severity of these events, clearly presented as a comparison between the emergency intervention and standard care. This includes data on length of hospital stay and whether or not suffering was increased or prolonged in contrast to the standard of care
- The outcomes for subjects in the placebo arm, if any
- Whether or not future research is indicated in the field of interest

There are some components of a scientific presentation that need not be present to a layperson audience. A detailed methods section and discussions of statistical tests and other technical details can be omitted in layperson disclosures. However such disclosures should make reference to scientific literature for those members of the public who would wish to access it.

Methods of disclosure

Informing the community in which the emergency research took place and the subjects and families of subjects who were involved in research of the results is not routine or familiar to researchers or sponsors. Therefore, required methods for such disclosure should be described in the FDA Guidance.

At a minimum, the methods used to meet the community consultation and disclosure requirements prior to conducting the research should be used to distribute the research results, including newspapers, radio, and television, flyers in public buildings (i.e. libraries, city/town hall) and in local clubs, community centers, and places of worship. Copies of the written laypersons' documents should be available at these locations for distribution to people in the community. Layperson results should be mailed to living subjects and immediate family members of deceased subjects. This will ensure that the subjects or their families understand the subject's involvement in the research and the outcomes of the entire research project.

Websites can be useful tools to reach a wide audience. The following parties' websites should contain a link to both the layperson and scientific results documents on their homepages:

- Hospitals in which the emergency research took place
- Industry sponsor
- City or town website, if available
- Associations interested in the particular research (i.e. American Heart Association website if cardiac emergency research was performed)

Page 21 – Legally authorized representative or family objection

The Draft Guidance provides that if a legally authorized representative or family member is available and the family member or legally authorized representative objects to the potential subject's entry into the study, that decision will prevail and the individual should not be entered into the study.

Interactions between researchers and "family members" will occur during stressful and emergent circumstances. The greater the clarity there is in defining the decisional authority of people close to the subject the more likely it will be that the incompetent subject's rights and welfare will be protected by someone who cares deeply about her or him.

While the definition of "family member" on page 24 of the Draft Guidance can be interpreted quite broadly and includes "any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship" we suggest that the Guidance should specifically state that same-sex relationships are included in the

category of those that are “the equivalent of a family relationship.” Additionally the Draft Guidance should categorically include “domestic partners whether of the same or opposite sex whenever such relationships are recognized by state law or by an employer for the purpose of providing health insurance coverage or any other employee benefit.”

Conclusion

We appreciate the opportunity to present our views to the Food and Drug Administration on this most difficult issue. We would be happy to clarify and expand upon any of the suggestions that we have made in this document.