

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 50, 56, 312, 314, 601, 812, and 814**

[Docket No. 95N-0158]

RIN 0910-AA60

Protection of Human Subjects; Informed Consent**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its current informed consent regulations to permit harmonization of the Department of Health and Human Services' (DHHS) policies on emergency research and to reduce confusion on when such research can proceed without obtaining an individual subject's informed consent. This regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The exception would apply to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them. FDA is taking this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized.

EFFECTIVE DATE: These regulations are effective November 1, 1996.

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SUPPLEMENTARY INFORMATION:**I. Background**

In the Federal Register of September 21, 1995 (60 FR 49086), the Secretary of Health and Human Services and the Commissioner of Food and Drugs proposed to amend FDA's current informed consent regulations to permit emergency care research. FDA proposed this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry

out at a time when the need for such research is increasingly recognized. By permitting certain adequate and well-controlled clinical trials to occur that involve human subjects who are confronted by a life-threatening situation and who also are unable to give informed consent because of their medical condition, the agency expects the clinical trials to allow individuals in these situations access to potentially life-saving therapies and to result in advancement in knowledge and improvement of therapies used in emergency medical situations that currently have poor clinical outcome.

FDA allowed 45 days for comment on the proposal of September 21, 1995. Written comments received in response to the proposal are on file in the Dockets Management Branch. Comments were received from clinical investigators, institutional review boards, patient advocacy groups, trade associations, professional societies, drug and medical device companies, and private citizens. The substantive comments received and FDA's responses are discussed below.

Approximately 90 comments were received on the proposed rule. The vast majority of these comments supported the proposal, although many of these comments contained suggestions or requests for clarification. A number of the comments that supported the proposal came from organizations and associations representing large numbers of members. These included the Brain Injury Association, the National Stroke Association, the American Academy of Orthopaedic Surgeons, the Coalition of Acute Resuscitation and Critical Care Researchers, Applied Research Ethics National Association, Pharmaceutical Research and Manufacturers of America, Health Industry Manufacturers Association (HIMA), the American Academy of Pediatrics, the American Heart Association Emergency Cardiac Care Committee, the American College of Emergency Physicians, the American Medical Association, the American College of Cardiology, the Society of Critical Care Medicine, the National Association of EMS Physicians, the American College of Obstetricians and Gynecology, and the American College of Physicians.

A number of the comments in favor of the proposal cited how it will facilitate research in this patient population, provide the necessary safeguards to ensure responsible and ethical research with protection of the human subjects, and ultimately speed the wide availability of products proven efficacious to individuals in life-threatening situations. For example, the American College of Physicians and the

Project on Informed Consent of the University of Pennsylvania Center for Bioethics commented that they "applaud these proposed regulations as a much needed step in the advancement of vital emergency research with careful attention to the rights and welfare of human research subjects." The American Heart Association commented that "We are particularly pleased with the balance that appears to have been struck between the need for conducting high quality clinical research in an effort to develop better treatments for critically ill patients and the protection of human subjects." The American Medical Association commented that "The proposed rules are far superior to their inadequate antecedents in balancing the need for emergency research with respect for the paramount concern for patient safety, welfare and comfort." The Brain Injury Association commented that "* * * this rule is a major step towards increasing the available therapies and medical care available for those individuals who are critically ill or injured." The Coalition of Acute Resuscitation and Critical Care Researchers commented that "* * * this proposed rule is a significant step forward towards advancing the medical care of critically ill or injured patients for whom current therapies are unsatisfactory or unproven." The National Stroke Association commented that "* * * once in practice it will help to appropriately expedite study enrollments thus allowing for earlier study completion, analysis, and ultimately will speed the availability of those drugs proven efficacious to the one-half million people who suffer stroke each year."

These comments are addressed in more detail in sections II and III of this document.

Generally, the 16 comments opposed to the proposed rule were from individuals who were not convinced by the agency's description of the legal and ethical basis for the rule, and these comments concluded that informed consent should not be waived under any circumstances. Some of these comments suggested that the agency was proceeding hastily and under undue pressure from the research community. In section II of this document, we address the general comments first, followed by the more specific comments.

II. General Comments**A. Need for the Rule**

1. One comment questioned the need for the rule and whether there were hard data documenting the number of

subjects eligible for these types of research activities who are lost to enrollment due to an inability to obtain informed consent from the subject or the subject's authorized representative. Another comment questioned the need for this rule based on the DHHS waiver granted in July 1995 for a hypothermia study, arguing that: (1) The waiver was not needed to complete a reasonable preliminary sample, (2) the criteria for participation were needlessly inclusive, (3) the investigator used questionable tactics to achieve waiver, (4) the provisions for oversight were inadequate, and (5) the provisions for monitoring were inadequate. This comment went on to discuss "the overarching considerations" for the rule, arguing that it is not in the subject's interest to prevent death in order to linger in a vegetative state; that the high percentage of families agreeing to continuing participation in the research after the fact demonstrates how ill-informed they are about the possibility of negative outcomes, e.g., prolonged vegetative state, dissipation of financial resources, court challenges to terminate life support; that subjects will be misenrolled in "an abundance" of life-threatening situations; that the rule does not address or provide for followup or special circumstances for terminating life support for "saved" individuals in these studies; and that it is not clear who will bear the cost and burden to sustain an individual who has been "saved" from a life-threatening medical condition by being on a research study.

The preamble to the proposed rule extensively discussed why this rule is needed and why this limited class of research has been unable to proceed under existing requirements. The purpose of this rule is to permit the study of potential improvements in the treatment of life-threatening conditions where current treatment is unproven or unsatisfactory, in order to improve interventions and patient outcomes. It is not the goal of this rule to leave study subjects in vegetative states or to have any of the other negative outcomes outlined in the comments. The risks to patients of having these negative outcomes exist now with interventions that are unproven or unsatisfactory. If interventions are improved, patient outcomes will be improved. The possibility of worsened outcome or adverse reactions will be assessed before the clinical investigation begins by the IRB and during the investigation by the data monitoring committee that is required under the regulation. The regulations require the institutional review board (IRB) to ensure that risks

to subjects are minimized and to determine that risks to subjects are reasonable in relation to anticipated benefits to subjects (see § 56.111(a)(1) and (a)(2) (21 CFR 56.111(a)(1) and (a)(2)), respectively). The rule does not address the issue of terminating life support because this is dictated by State law and is implemented through such standard procedures as "do not resuscitate" orders.

B. Ethical Objections to the Rule

2. Several objections to the proposed rule noted that the major protection from research risks remains informed consent and that without this procedure, potential abuse of research subjects will always remain unacceptably high; that it is unethical for patients who cannot consent to receive nonstandard care; that overriding individual autonomy and not obtaining informed consent is unacceptable; that therapeutic intent is not sufficient to obviate consent when there are no data or when there is uncertainty or disagreement. Some of these comments mentioned the recent report of the President's Advisory Committee on Human Radiation Experiments, in which radiation experiments without the subjects' consent are condemned as a wrongful use of persons as means to the ends of others; others mentioned examples from Nazi Germany, Stalin's U.S.S.R. and other totalitarian regimes. Some of these comments noted that it is particularly objectionable that there is no way to avoid involvement as a subject in this research if, as an individual, one objects to the research.

The agency acknowledges that the waiver of informed consent is a serious matter. That is why it has developed a regulation that requires additional protections when informed consent is waived. The purpose of this rule is to ensure such protections.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research states in *The Belmont Report* that:

Respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

This rule, § 50.24 (21 CFR 50.24) in part 50 (21 CFR part 50), can be invoked for emergency research in which it is not feasible to obtain informed consent from prospective subjects. As such, these

subjects have diminished autonomy and are entitled to protection. *The Belmont Report* states that:

The extent of protection afforded [to individuals with diminished autonomy] should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

The Belmont Report, thus, states that: (1) Subjects with diminished autonomy are entitled to protection; (2) the extent of protection should depend upon the risk of harm and the likelihood of benefit; and (3) the judgment that any individual lacks autonomy should be periodically reevaluated. This regulation incorporates each of these principles.

The regulation recognizes that subjects with diminished autonomy are entitled to protection. These additional protections include the requirements in the regulation for consultation with representatives of the communities from which the subjects will be drawn; public disclosure of the clinical investigation and its risks and expected benefits prior to initiation of the investigation; public disclosure of sufficient information following completion of the investigation to apprise the community and researchers of the results of the investigation; the establishment of a data monitoring committee to exercise oversight of the investigation; and, if consent is not feasible and a legally authorized representative is not available, providing an opportunity for a family member to object to a subject's participation in the investigation, if feasible within the therapeutic window.

The regulation recognizes that the extent of protection should depend upon the risk of harm and the likelihood of benefit to the subjects. The regulation requires the IRB to find and document that appropriate animal and other preclinical studies have been conducted; that the information derived from those studies and related evidence support the potential of providing a direct benefit to the individual subjects; and that the risks associated with the investigation are reasonable in the light of what is known about the prospective subjects' medical condition, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

The regulation recognizes that the judgment that any individual lacks autonomy should be periodically reevaluated. This is reflected in two requirements: (1) The IRB must review and approve informed consent

procedures and an informed consent document for use with subjects or their legal representatives in situations where use of such procedures and documents is feasible; and (2) at the earliest feasible opportunity, each subject (or a legally authorized representative or family member) will be informed of the subject's inclusion in the research, the details of the research, and that the subject (or representative or family member) may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

In response to the comments that expressed concern about the ability of an individual to avoid involvement as a subject in this research, the agency thinks that the opportunity for individuals to express objections to the research may be optimized in a number of ways. Comments suggested making available medical bracelets that record refusal to participate in the research, and publicizing the existence of the bracelets; and excluding from participation those individuals with advance directives rejecting such research (most feasible for hospitalized patients). The agency encourages IRB's, investigators, and sponsors to work together to maximize the ability of individuals to prevent their inclusion in research to which they would object. The agency does not believe that this rule creates a situation that differs significantly from other emergency situations warranting intervention in that individuals in life-threatening situations are often unable to direct decisions concerning their health care and are, therefore, unable to consent or object to a particular treatment. Yet they are routinely treated by State-licensed medical practitioners. This inability to exercise autonomy is not unique to the subjects who will be eligible for this research—it is common to the majority of individuals who may be in these life-threatening situations.

FDA thinks that the protections contained in this rule including IRB review, the requirements for obtaining informed consent when it is feasible, and for community consultation and disclosure will prevent unethical research from occurring.

FDA expects these procedures involving waiver of informed consent to be used infrequently. As noted, the research carried out under such a waiver must present the potential of direct benefit to the individual subjects. It should be initiated only after appropriate animal and other preclinical studies have been conducted, and it is clear that the information derived from those studies and related evidence

support the potential of direct benefit to the individual subjects.

3. One comment stated that the proposal violates the American Hospital Association's "Patient's Bill of Rights" to fully informed consent.

The agency has reviewed the AHA's Patient's Bill of Rights and concludes that there is no conflict between this rule and that document. In particular, the agency notes that the Patient's Bill of Rights recognizes that an exception occurs "in emergencies when the patient lacks decision-making capacity and the need for treatment is urgent."

4. Another comment questioned the agency's discussion of respect for persons in the preamble to the proposal and the agency's supposed conclusion that if individuals capable of exercising their autonomy refuse to enroll in research, this justifies diminished protection to those individuals who lack the capacity for autonomous choice. This comment defined the informed consent doctrine as: (1) Promoting individual autonomy; (2) respecting human dignity; (3) encouraging professional self-scrutiny; (4) promoting rational decisionmaking; (5) avoiding deceit and coercion; and (6) educating the public. It then concluded, that by exempting emergency research from informed consent, the agency was concluding that these values have no relevance to decisions made in the context of emergency research.

This comment misrepresents the agency's discussion of the principle of respect for persons. In the preamble to the proposed rule, the agency described:

[H]ow the principle of respect for persons incorporates two general rules of ethical behavior: (1) Competent individuals must be treated as autonomous agents * * *; and (2) persons whose autonomy is absent or diminished may participate in research only if additional protections are provided for them.

(60 FR 49086 at 49093, September 21, 1995)

This rule, in fact, incorporates the values described in the comment to the extent that they are relevant to decisions made in the context of emergency research.

5. A number of comments misinterpreted the agency's description of the principle of justice in the preamble to the proposed rule, and were offended by the idea that it is acceptable for a researcher to waive consent because if consent were requested, it would be refused. One comment suggested that the agency clarify that it meant that it is often easier to locate legal representatives from white populations than from minority populations, and for that reason if

consent were required from a legally authorized representative, the requirement could prevent equitable numbers of minority patients from having the opportunity to participate in emergency research. The Indian Health Service recommended that the agency supplement its discussion of justice by adding the following:

Waiving informed consent will increase justice only in communities or sub-communities with a low percentage of people who would refuse to participate if asked. Many minority or economically disadvantaged communities distrust research more, and have higher percentages of refusers, than white middle class communities; in such communities, the ethical principle of justice would favor maximizing self-determination (i.e., informed consent) over achieving high rates of participation. Justice would also require the public disclosure to and consultation with those communities as required in the Proposed Rule; if those communities do not agree to be sites, consideration should be given to doing the research elsewhere.

The Indian Health Service, in supporting the intent of the rule, articulated two aspects of the problem: (1) Finding legally qualified surrogates for individuals who lack telephones, for example, which is a socioeconomic barrier; and (2) a surrogate's unwillingness to enroll a relative in the research, based on distrust of research and researchers. If certain communities have a higher prevalence of refusers than others, the ethical harm of inadvertently enrolling people in research against their will would fall on those communities with a higher prevalence of refusers. Thus, the Indian Health Service (IHS) concluded that while it may be appropriate to waive informed consent based on socioeconomic barriers, it is not appropriate to waive informed consent in communities in which there are lower rates of obtaining surrogate consent due to the unwillingness of surrogates, i.e., high refusal rates. Another comment noted that if the community in which an emergency research study is carried out has a large minority and lower income population, then the likelihood of the community agreeing prospectively to participate in the study would be small or nonexistent; ethically this would violate the principle of justice in that such communities would be unlikely to share the burdens and benefits of participation in such research.

The agency's comments concerning justice, in the preamble to the proposed rule, concerned the ability of health care delivery personnel to locate legally authorized representatives. The agency agrees with the IHS articulation of the

two aspects of the problem. The agency would not consider writing a rule that would permit the waiver of informed consent in a situation where if consent were requested, it would be refused. Such an action would violate ethical principles.

The agency has implicitly addressed the problem of a surrogate's unwillingness to enroll a relative in research through the rule's requirement for community involvement, including consultation with and disclosure to the community, and by providing that consent from the subject or the subject's legally authorized representative be obtained or an opportunity for a family member to object be provided when it is feasible.

If an IRB decides that its community should not participate in research, the agency does not believe that decision would violate the principle of justice. Justice, in this context, requires only that the community have the opportunity to participate in the research if asked.

C. Harmonization

6. A number of comments applauded the intent of FDA and DHHS to harmonize regulations in this area. Concern was expressed, however, that because FDA and DHHS did not propose regulations simultaneously, the two regulations may not ultimately be identical, thus thwarting a major objective of this endeavor. One comment expressed concern that the DHHS waiver might follow the specific project waiver for hypothermia research that was published in July 1995, that, according to the comment, was not sufficiently protective of subject rights. Another comment suggested that for studies that do not involve drugs or devices, DHHS develop an analogous mechanism to FDA's requirement that studies be submitted for agency review. Another comment suggested that the two sets of regulations not be in total harmony in this regard, because a greater degree of protection of subjects is necessary for studies of drugs and devices that are not yet FDA-approved, than for those involving drugs or devices that have received approval. One comment encouraged FDA and the Office for Protection from Research Risks (OPRR) to work together to ensure that current Multiple Project Assurances remain valid and not require renegotiation as a result of this rule.

DHHS has committed to consistency between the FDA final rule and the Secretarial waiver of the DHHS regulations in all critical respects. Elsewhere in this issue of the Federal Register is the Secretarial waiver of the

DHHS regulations for the protection of research subjects for emergency research. The agency notes that FDA's rule requires investigational new drug applications (IND's) and investigational device exemptions (IDE's) for all clinical investigations involving drugs and devices seeking an exception to the requirement for informed consent, including both those that have received marketing approval and those that have not.

7. Other comments asked for clarification as to whether the requirement contained in § 50.24(d) would apply to studies that attempt to elucidate a pathophysiologic explanation (e.g., blood drawing studies); studies that use interventions of different techniques (e.g., two different methods of bystander CPR); research designed to explore basic pathophysiological mechanisms in emergency situations; studies to compare the timing of standard fluid administration for shock and surgical techniques; etc. If FDA's regulation did not apply, these comments asked if the DHHS "harmonized" regulation would apply to these studies and require prior DHHS review or whether some other agency would be responsible for prior review of the proposed research.

These regulations are applicable only to clinical investigations involving products that are regulated by FDA. The DHHS regulations apply to research supported or conducted by the Department or conducted in an institution that has agreed to review all research, regardless of its funding source, in accord with the DHHS regulations. The "harmonized" regulations have compatible criteria; their basic requirements are in agreement. FDA includes terms specific to the type of research covered by FDA regulations (e.g., it uses the term clinical investigation instead of research). Both the DHHS and FDA recognize that there may be research that is neither regulated by FDA nor supported or conducted by DHHS; for that research, it is possible that neither regulation will apply.

D. Comment Period and Effective Date

Several comments opposed to the regulation objected to the 45-day comment period and the agency's proposal that the final rule will be effective upon publication.

8. One comment suggested that the effective date of the regulations should be 30 days after publication of the final rule. This comment noted that this research has been halted since mid-1993, that all parties will need time to develop adequate policies and procedures to comply with the new

rule, and that distribution of the policy to those affected will take up to 30 days.

The agency agrees with this comment and has made the effective date of the final rule 30 days after its publication in the Federal Register. The agency notes that the Secretarial waiver of the DHHS regulations, published elsewhere in this Federal Register, is also effective 30 days after its publication. IND's and IDE's that intend to invoke this rule may be submitted to the agency on or after its publication date and should include a description of how the clinical investigation proposes to meet the conditions of this regulation. These investigations cannot begin until the rule is effective, the agency has reviewed the investigation against the requirements contained in this final rule, a letter has issued to the sponsor advising the sponsor that the investigation may proceed, the investigation has been reviewed and approved by an IRB, and the community consultation and disclosure required by this rule have occurred.

9. Comments objecting to the 45-day comment period suggested that there was inadequate time to discuss the proposed changes in the regulation at length with a broader audience, that the IRB community is ill-informed about the proposed rule change and therefore the comment period should be extended, the issue revisited, and the rule reconsidered. One of these comments stated that the process leading to development of the rule was flawed and that it appears that the comment period is irrelevant, that no significant review of the basic issues will occur, and, thus, the rule is a *fait accompli*.

As described in detail in the preamble to the proposed rule, the issues associated with this rule were debated at length at conferences, during FDA and NIH cosponsored Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, at a congressional hearing, and in various articles. The agency received no formal request for a general extension of the comment period; instead, it received numerous thoughtful comments and has modified the proposed rule as a result of those comments. 21 CFR 10.40(b)(2) states that a proposed rule " * * * will provide 60 days for comment, although the Commissioner may shorten or lengthen this time period for good cause. In no event is the time for comment to be less than 10 days." In the proposed rule, the agency explained why the Commissioner determined that there was good cause to shorten the comment period from 60 to 45 days.

In order to encourage comments on this rule, the agency conducted a number of out-reach efforts to publicize publication of the proposal. The agency provided information on the proposed rule to national media and trade press contacts. The agency mailed copies of the proposal to all registrants at the January 1995 Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances and to over 1,000 IRB's and over 250 health professional organizations and consumer groups. FDA also distributed copies at workshops and at national meetings of IRB organizations. The agency invited consumer, health professional, and industry organizations to briefing meetings where the proposal was described and questions could be answered. The agency encouraged the submission of comments to the administrative record maintained by the Dockets Management Branch whenever possible.

E. Preemptive Effect

10. In the preamble to the proposed rule, FDA requested comment on the need to preempt local and State regulations. The agency received a number of comments both for and against the need for preemption.

Comments received that were opposed to preemption included the following: There is no legitimate (constitutional) over-riding Federal concern that requires the Federal Government to preempt local and State requirements; it is inappropriate to remove the ability of citizens to enact State and/or local laws that would require additional protections for research subjects, or to restrict the conduct of this type of research if citizens find it objectionable based on community standards; it is not logical to prohibit local action when the regulation itself emphasizes community involvement and deference to community standards.

The IHS objected to Federal preemption because it would: (1) Counter the long-standing Federal policy not to place restrictions on tribal sovereignty; (2) be an unnecessary limitation, because retaining tribal sovereignty would have no measurable adverse effect on the nation or on emergency research as a whole; (3) give American Indian and Alaska Native (AI/AN) people and governments one more reason to distrust the Federal Government, because they would see the rule as putting AI/AN people at risk for the good of non-AI/AN people and communities; and give AI/AN people and governments one more reason to distrust research, because they would

see the rule as overriding a patient's or family's desire not to participate in research—a desire more common in AI/AN communities than in white middle class communities.

Other comments noted that the proposal did not recognize tribal sovereignty and that it undermines the tribal government's authority to implement stricter requirements for biomedical research conducted on persons residing in tribal jurisdictional boundaries. Comments noted that the tribal review process is in place to protect tribal members from unnecessary or undesirable research.

Another comment opposed to preemption noted that the rule would preempt State and local laws for the minimum protections acceptable for emergency research involving waiver of informed consent; however, without preemption, it permits greater protections to be imposed at the State or local levels. One comment suggested that in lieu of preemption, FDA and IRB's should track how States, local, or tribal governments retain or amend their laws in response to public discussion by researchers with those governments and assess the various reactions after 3 years.

Other comments supported the need for preemption in order to ensure national uniformity; to prevent or limit liability of universities, hospitals, IRB members, clinical investigators, and sponsors for failure to provide informed consent under State law or in the event of a poor subject outcome; and to enhance the ability to conduct valuable research with critically ill subjects. These comments stated that the subject protections included in the proposed regulation are substantial enough to justify Federal preemption of State and local law, and that current State laws (e.g., in the State of Florida) would preclude research that otherwise could be authorized by IRB's under these rules. Several comments supported the need for preemption, noting the difficulty caused by differing State laws that define who may serve as a legal representative or that are ambiguous on this issue. Another comment noted that without Federal preemption, Federal uniformity in the application of waiver of informed consent in a specific setting will not occur. This comment argued that Federal preemption would: (1) Forestall wasteful State court litigation to explore whether the scope of the privilege of emergency action without consent is consistent with the proposed Federal rule, and any related potential liability; and (2) implement congressional intent to create nationally

uniform criteria for informed consent and research involving human subjects.

The Coalition of Acute Resuscitation and Critical Care Researchers surveyed a number of State representatives regarding State regulations for informed consent for research and identification of surrogates. The results of that survey (with 19 States represented) indicate that there are very few States that have specific legal requirements pertaining to waiver of consent for research.

The agency has carefully considered each of these arguments in support of, and opposed to, preemption of State law. The agency has concluded that it would be inappropriate to preempt State law at this time. Preemption of State law would prevent the application of State or local law that requires additional protections to research subjects and, as such, would be inconsistent with the existing Federal policy for the Protection of Human Subjects and the DHHS regulations (45 CFR 46); in addition, it would be inconsistent with the notion of community norms, upon which this regulation is based.

F. Followup/Reassessment

11. One comment recommended that the implementation of this rule be assessed in 3 years and that any pending questions be addressed during the assessment. Another comment asked the agency to announce its intent to survey and analyze the experience with the rule following 3 years of implementation. The comment recommended that the rule encourage IRB's and researchers to track implementation information including: The number of times the researcher was able to contact legally authorized representatives within the allowed therapeutic window time period; problems with the documentation and procedures used for the consent process with those representatives; the percentage of subjects or legally authorized representatives who wanted to discontinue the intervention or to remove their data from the research database in the posthoc debriefing; problems with documents and procedures used to give the community the preresearch public information and the post-research information; and problems with the documents and procedures for consulting with community representatives. This comment suggested that this information be described both as seen by the IRB and by the experienced researcher.

The agency agrees that it will be important to assess implementation of this rule and, thus, the agency intends to evaluate implementation of this rule

on an ongoing basis. The agency believes that a sponsor's IND or IDE and new drug application (NDA), product license application (PLA), or premarket approval application (PMA) should contain sufficient information under the agency's existing reporting and recordkeeping requirements for the agency to assess how well this rule is working without requiring additional information collection and recordkeeping by researchers and IRB's of their experiences under the rule. The agency, however, encourages IRB's, researchers, and sponsors to share their experiences under this rule, for example, in publications and at conferences, so that the research community and public can benefit from their experiences. The agency notes that for research that is regulated by FDA, although subjects, legally authorized representatives, or family members may elect to withdraw from continued participation in the clinical investigation, they may not remove previously collected data from the research database because it is critical that FDA obtain and be able to consider all data on a product's use in order to be able to determine its safety and efficacy.

G. Scope/Applicability

1. Special Populations

12. One comment questioned the applicability of this rule to specific special patient populations. This comment recommended that FDA rule state that it does not apply to research involving prisoners or fetuses; and urged that the decision about its applicability to emergency research targeting pregnant women be made after the DHHS regulations have been revised and the 3 year period in which experience of implementing the rule will be obtained and analyzed. This comment recommended that pregnant women should not be excluded from emergency research. This comment also recommended that the rule state that it does not apply to children now; rules for pediatric emergency research should be developed by the end of the 3 year period of experience and assessment; and noted that the process of Secretarial waiver is available if an exception for a specific pediatric emergency protocol must be made before then.

Taking a contrary view, the American Academy of Pediatrics stated that:

* * * it is important that children be included in research protocols, including those on emergency treatments, so that the safety and efficacy of various treatment methods can be determined in a scientific manner. We believe that this proposed

regulation will help to further that objective while protecting children as much as possible by requiring that a consent document be available in cases where surrogate permission can be obtained in a timely manner.

The agency believes that it would be inappropriate to exclude any special subject population from this regulation. Moreover, for research regulated by FDA, a Secretarial waiver of the informed consent requirement may not be an option. Thus, the agency is not limiting the applicability of this regulation to exclude any special subject population. The agency notes that it is the general responsibility of the IRB, where some or all of the subjects are likely to be vulnerable to coercion or undue influence, to ensure that appropriate additional safeguards have been included in the clinical investigation to protect the rights and welfare of these subjects. (See 21 CFR 56.111(b).) The subject population covered in this rule is, in a sense, a particularly vulnerable population, by having no capacity to decide about medical treatments. The additional safeguards in the rule are included for this reason.

2. Existing Regulations

13. One comment asked the agency and DHHS, respectively, to explicitly state, when this rule is finalized, that FDA will retain § 50.23(a) (21 CFR 50.23(a)) and the DHHS will retain 45 CFR 46.116(d).

Both FDA and DHHS will retain these sections in the Code of Federal Regulations. These sections will continue to be useful in situations not otherwise covered by this regulation.

14. Another comment suggested that the regulations address compensation or medical treatment available in the event of unanticipated injuries or death.

The agency agrees that it is important for all subjects in a clinical investigation to be provided with the basic information required by § 50.25, including § 50.25(a)(6) that requires that information be provided to each subject about whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. As a result, the agency has modified § 50.24(a)(6), previously numbered § 50.24(a)(5), to make it clear that the IRB-approved informed consent document must be consistent with § 50.25. The agency has also modified § 50.24(b) to make it clear that when prospective informed consent cannot be obtained, the subject, or the subject's legally authorized representative or family member is to be informed, at the

earliest feasible opportunity, of the subject's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document.

15. A third comment requested the agency to retain two protections previously established by the agency that are not contained in the proposed rule: (1) That the intervention be in the health interest of the subjects; and (2) that an attempt to obtain informed consent be made and documented for enrolled research subjects by a physician unaffiliated with the research activity.

The agency thinks that the concerns expressed by the first protection are addressed in § 50.24(a)(3), which requires that participation in the research hold out the prospect of direct benefit to the subjects. The second protection is similar to that contained in § 50.23(a), which requires, in effect, a second opinion from a physician who is not otherwise participating in the clinical investigation that the conditions for waiving informed consent are met. This protection is performed for the class of subjects in this research by the requirement in § 50.24(a)(2) that a determination be made that obtaining informed consent is not feasible and that this determination receive the concurrence of a licensed physician who is either an IRB member or a consultant to the IRB, and who is not otherwise participating in the clinical investigation (§ 50.24(a)). The agency notes that § 50.24(b) requires that at the earliest feasible opportunity, each subject is to be informed of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The agency also notes that under new § 50.24(a)(5), the researcher is required to describe the efforts made to obtain informed consent and make this information available to the IRB at the time of continuing review.

3. Foreign Data

16. One comment noted that the rule was silent as to its potential impact on the acceptability of data generated in emergency research studies that are not subject to the proposed rule—i.e., studies conducted outside the United States and outside the scope of the IND and IDE regulations. This comment asked FDA to make it clear that such studies will continue to be considered acceptable in terms of providing evidence of safety and effectiveness and could be treated as pivotal trials, even though they may not meet some of the proposed requirements for the conduct

of emergency research. This comment stated that if this clarification is not consistent with the agency's intent, then the proposal effectively establishes a new, inappropriate standard concerning the adequacy of clinical studies for purposes of providing evidence of safety and effectiveness that would require specific notice-and-comment rulemaking.

Sections 312.120 and 814.15 (21 CFR 312.120 and 814.15) describe the criteria for acceptance by FDA of foreign clinical investigations not conducted under an IND and IDE, respectively. In general, FDA accepts such clinical investigations provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. FDA will accept such emergency research investigations provided that they meet the requirements of § 312.120 and § 814.15. This rule does not change the requirements of § 312.120 and § 814.15.

17. One comment noted that the International Conference on Harmonisation Draft Guideline on Good Clinical Practice (GCP) (60 FR 42948, August 17, 1995) states that "the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over [the] interests of science and society." This comment suggested that the main argument for the proposed rule is for the benefit that the new drugs and devices will bring to science and society, rather than recognizing, as the GCP does, the value of the individual and subject rights.

The agency disagrees that this rule is inconsistent with the ICH Draft Guideline and has emphasized in the preamble to this regulation that the basic rationale for this rule is that it holds out the prospect of direct benefit to the subjects. The agency is committed to protecting the rights of research subjects. In addition, FDA recognizes that this rule may also serve society by making available more drugs and devices for use in emergency, life-threatening situations. The agency notes that the draft GCP cited specifically acknowledges the need for waivers of informed consent in some circumstances.

4. Independent IRB's

18. One comment expressed concern about FDA's continued acceptance of reviews by "independent" IRB's. This comment questioned the ability of a nonlocal, independent IRB to have local insight and knowledge necessary for comprehensive review and continuing

oversight, and suggested that unless there is monitoring of independent IRB's by OPRR, they should not be allowed to approve research under this rule. The agency received other comments asserting that independent IRB's are well-qualified to maintain the requisite oversight and responsibilities of emergency research trials and that independent IRB's can maintain ethical standards equivalent to dependent IRB's.

As previously discussed in the preamble to the proposed rule, the agency thinks that independent IRB's can properly review this type of research. The agency thinks that duly constituted IRB's can ensure that the rights and welfare of research subjects are protected by fulfilling the requirements of part 56 (21 CFR part 56) and § 50.24, including § 50.24(a)(7) requiring public disclosure as well as consultation with the communities from which the subjects will be drawn. FDA anticipates that this type of research will usually be performed in an institution with an IRB. In that case, the IRB for the institution has the responsibility and authority to review all studies performed in the institution. This review responsibility may not be delegated to another IRB unless the institution and the IRB for the institution agree to the delegation and the agreement is documented in writing.

5. Conflicts with Statutes, the Constitution, and Other Standards

19. One comment stated that the rule conflicts with State common law—that is, a physician who performs research without obtaining consent for that research will be liable under common law for malpractice and battery, and is likely to lose his or her license. This comment stated that by adopting the proposed rule, FDA is overstepping its authority by attempting to regulate the practice of medicine and by attempting to override State law, and that FDA lacks the authority to permit anyone in the medical profession to practice without obtaining consent.

FDA disagrees with the comment. This rule does not attempt to regulate the practice of medicine. Rather, as discussed more fully in the preamble to the proposed rule, FDA is regulating investigational products under the statutory authority contained in the Federal Food, Drug, and Cosmetic Act (the act). FDA also disagrees with the comment that FDA is overriding State law. As stated elsewhere in this preamble, FDA is not changing the existing Federal policy that recognizes the continuing validity of applicable State or local laws and regulations on

human subject protections. With regard to physician liability for performing research under this regulation, FDA disagrees with the comment's blanket conclusion that physicians participating in such research are committing malpractice and battery. FDA notes that this rule does not override existing State and local laws and regulations that may apply to such research. Institutions wishing to participate in such research may wish to consult their attorneys regarding any State and local restrictions that preclude such research. As with other research, physician liability for activities engaged in during emergency research will vary from State to State because of different laws on human subject protections. FDA notes that an existing regulation § 50.23 permits waiver of informed consent in certain limited emergency situations. FDA is unaware of any research conducted in accordance with that regulation that has resulted in physician liability for malpractice or battery.

20. One comment stated that the proposal violates Federal law under the Patient Self-Determination Act of 1990.

FDA disagrees with the comment. The Patient Self-Determination Act of 1990 defines an advance directive as "a written instruction, such as a living will or durable power of attorney for health care, recognized under State law (whether statutory or as recognized by the courts of the State) and relating to the provision of such care when the individual is incapacitated." (42 U.S.C. 1395cc(f)(3).) That act imposes obligations on certain facilities (hospitals, skilled nursing homes, home health agencies, and hospice programs) participating in the Medicare program regarding advance directives. (42 U.S.C. 1395cc.) The Patient Self-Determination Act requires these facilities to give information to patients about their rights under State law to accept or refuse treatment and to make advance directives. These facilities also are required to document in the patient's medical records whether the patient has executed an advance directive and to ensure compliance with State laws on advance directives. The comment did not explain how he believed the rule violates the Patient Self-Determination Act; nothing in this rule prevents facilities from continuing to act in compliance with the requirements contained in that act.

21. Another comment questioned the validity of the claim in the proposal that "the proposed rule gives double weight to the statutory 'necessitates' criterion" because "(1) intervention is needed because of the medical condition, and (2) the collection of valid data is needed

because of the absence of proven satisfactory available treatment for the condition." This comment stated that the context of the "necessitates" clause makes it clear that what is necessary is the use of a device to preserve the life of the subject—that the relationship of necessity is between the intervention and the subject's condition. This comment stated that it is a perversion of the statutory language to claim that it uses "necessitates" to refer to the relationship between the collection of data and proven treatment. The comment noted further that randomly assigning subjects to a treatment that some researchers consider unsatisfactory and to a treatment researchers think may be an improvement is not necessitated by the subject's life-threatening condition and, further, a placebo can never be necessitated to preserve a subject's life.

The agency agrees that the "necessitates" clause focuses on the relationship between the treatment and the subject's condition. The idea that an intervention using an investigational product is "necessary" may, at first, appear to be contradictory. It does not mean the product is safe and effective and that it must be given to everyone. Read this way the exception would apply to products that are not investigational and it would be irrelevant. The device amendments to the act are referring to an investigational intervention that is not known to be beneficial, and "necessitate" means that because available therapy is inadequate, potentially beneficial intervention is needed. Thus, there is no obligation to give everyone the investigational intervention despite the patient's need for some better treatment; it is possible to give only some subjects the intervention, leaving others to the care they would get were there no study. In the absence of an obligation to give every patient the investigational intervention, it is possible to consider other factors, such as the need to evaluate the intervention and learn from the exposure, which potentially may benefit the subject in the study, the community, and future patients with the disease. The critical and potentially difficult concept is that the intervention is given because the patient/subject needs it, yet enough is not known about the intervention to support giving it to everyone as therapy.

It is clear, despite the uncertainty, that the investigational intervention is intended to be beneficial and that there is conceptual, preclinical, and possibly clinical (e.g., other settings, preliminary results) evidence that the hoped for benefits outweigh the potential risks, all

of which leads the investigator (and the pertinent IRB) to hope for, even anticipate, benefit. Such anticipation is compatible with the state of clinical equipoise needed to allow a clinical investigation. Indeed, true neutrality is rarely present at the start of an investigation; in the absence of expectation that an intervention may represent an improvement, or a belief that a standard therapy might not work, there is little incentive to proceed. The experienced clinical investigator, however, also knows that expectations are not the same as knowledge and that disappointments are too common to ignore. Therefore, despite optimistic expectations, one can be in the state of equipoise needed to allow a clinical investigation to be conducted.

In the current rule, addressing the special case of nonconsenting subjects, the agency is asking for more than the usual assurances that the investigational intervention is promising, and that accumulating results have not taken us all the way past equipoise (through the data monitoring committee's considerations). This extra assurance is necessary because it must be possible to state honestly that the intervention is for the patient's benefit, at least at the level of being promising, and is not a project only for pure science, future generations, or the community, although it will, of course, benefit those too.

Therefore, if there are available only unproven or unsatisfactory therapies and appropriate animal and other preclinical studies support the potential of benefit to subjects from a new intervention, the agency thinks it can be said that the subject's condition "necessitates" alternative treatment. In the case under consideration, where the new intervention is not known to be of value, although it is promising and has been evaluated in animals and in less emergent settings, it is reasonable to randomize to a standard therapy not yet shown inferior to the new intervention. The subject receiving standard therapy is no worse off than if there had been no clinical investigation.

22. Another comment considered the rule contrary to the Nuremberg Code and to the U.S. Constitution; it stated that the agency's reliance on *Doe v. Sullivan* is inappropriate. Another comment suggested that the decisions of the U.S. Supreme Court in *Cruzan v. Director Mo. Department of Health*, and *Griswald v. State of Connecticut* present constitutional barriers to the proposal to eliminate the requirement of informed consent in biomedical research involving emergency conditions. This comment also analyzed an attorney's observations at the Public Forum with

respect to State law and criticized the proposal for not addressing these. Another comment stated that the rule denies persons with disabilities equal protection under the law and their rights to due process in that it treats competent and incompetent patient-subjects in a distinct, unequal manner.

FDA disagrees with these comments and with the assertions that the cases cited present constitutional barriers to the issuance of this rule. FDA strongly endorses the concept of informed consent. Obtaining informed consent is not always possible, however, as Congress has recognized in enacting amendments to the Act. Congress explicitly has authorized exceptions from the requirement for informed consent in research in limited situations. (See preamble to the proposed rule for a more detailed discussion of authority in the act for permitted exceptions from informed consent (60 FR 49086)).

Unlike situations involving a failure to inform a competent person of the risks and consequences associated with participating in research (see *In Re Cincinnati Radiation Litigation*, 874 F. Supp. 796, 800-01 (S.D. Ohio 1995)), this rule seeks to maximize an individual's access to potentially beneficial drugs and devices at a time when, due to an emergency which causes incompetency, informed consent cannot be obtained. The issuance of this rule does not result in the automatic entry of an individual in a clinical investigation without informed consent. Rather, it contains important protections that must be met before such a clinical investigation may proceed. Decisions on whether an investigation may proceed will be made on a case-by-case basis by individual IRB's and need the concurrence of a licensed physician.

Contrary to the comment's suggestion, the Supreme Court's decision in *Cruzan v. Director Mo. Department of Health* does not create a hurdle to the issuance of this rule. In *Cruzan v. Director Mo. Department of Health*, 497 US 261 (1990), the Supreme Court, in reviewing a Missouri statute which required clear and convincing evidence of an incompetent person's wishes as to whether or not life-sustaining treatment should be employed, balanced a State's interest in the preservation of life with an individual's wish to terminate life support rather than remain in a vegetative state. Unlike *Cruzan*, this rule focuses on the preservation of life when an individual's wishes are unknown. As in other emergency situations, where an individual is incompetent, if it is feasible to obtain informed consent from the individual's legally authorized

representative, then such consent should be obtained. FDA notes that it is possible that an individual may have previously issued advance directives on life-sustaining treatment. FDA believes that, where feasible, attempts should be made consistent with State law to identify the existence of such directives prior to enrolling an individual into a clinical investigation without informed consent. FDA recognizes, however, that in many life-threatening instances it may not be feasible to learn of the existence of any existing directives prior to taking potentially life-saving intervention and that in many instances, an individual may not have issued such advance directives. In such cases, FDA believes that interventions consistent with this rule are constitutionally permissible.

H. Clarifications

23. HIMA noted that it was one of the organizations that endorsed the October 25, 1994, consensus document on Informed Consent in Emergency Research from the Coalition Conference of Acute Resuscitation and Critical Care Researchers.

The agency acknowledges that HIMA endorsed the consensus document on Informed Consent in Emergency Research from the Coalition Conference of Acute Resuscitation and Critical Care Researchers.

24. HIMA also suggested that FDA recognize the diversity of opinion on "deferred consent" and its history of successful use from approximately 1980 until mid-1993, rather than simply disregard this concept as "post-hoc ratification" unworthy of "genuine" informed consent.

FDA disagrees and thinks that its earlier rejection of "deferred" consent was appropriate. As described in the preamble to the proposed rule, posthoc ratification is not genuine consent because the subject or representative has no opportunity to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use.

III. Specific Comments on the Proposed Regulation

A discussion of the specific comments received in response to this proposal follows:

A. Definitions

25. Four comments requested clarification of the proposed definition of family members in § 50.3. Two comments questioned what one should do if there is disagreement among family members. One asked whether a family member could provide informed

consent for emergency research if State law does not explicitly provide for consent from family members. Another questioned whether family members, even those who do not possess power of attorney for health care rights, can provide informed consent for emergency research under this rule.

One individual suggested that it may be unwise to provide a new definition for such a familiar expression as "family member" and suggested that the phrase "any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship" be used in its place. Another comment commended the agency for including in its definition those individuals whose relationship resemble family relationships.

One comment suggested that the hierarchy of the decision-making authority of family members should be clearly stated. This comment questioned whether one family member could overrule the decision of another and questioned whether all family members must agree.

The agency thinks that it is appropriate to retain the phrase "family member" and its definition. The agency has specifically included family members under this rule because the opportunity for an available family member to object to a potential subject's participation in such a clinical investigation provides an additional and an important protection to these individuals. Otherwise, if consent from a subject or the subject's legally authorized representative were not feasible, the eligible individual could be enrolled into the investigation. Thus, by permitting a family member (even one who is not a legally authorized representative) to object to an individual's inclusion in the investigation, a further protection is provided to that individual. This rule has been modified to make clear that a family member must be provided an opportunity to object to the potential subject's participation, if feasible within the therapeutic window when obtaining informed consent from the subject is not feasible and a legally authorized representative is not available. The agency recognizes that this may not constitute legally effective informed consent if the family member is not a legally authorized representative under State law. FDA is not establishing a hierarchy of family members although an IRB may consider the need for creating a hierarchy in reviewing individual investigations. Under this rule only one family member would need to be consulted and agree or object to the patient's participation in the

research. If family members were to disagree, the researcher and family members would need to work out the disagreement.

26. One individual, who was opposed to the entire rule, suggested that by not providing a definition of "emergency," FDA's quest for harmony and uniformity would be defeated by the various definitions provided by State law. He suggested that without such a definition, too much discretion is delegated to medical researchers and IRB's; that the agency will have little basis to monitor the activities carried out by these researchers; and that the exception will be used to exempt all emergency research from consent, even when it is feasible to prospectively identify and secure the consent of hospitalized individuals. Finally, he noted that the Health Care Financing Administration has issued regulations under the Emergency Medical Treatment and Active Labor Act which define the term "emergency medical condition;" this act's regulations link an emergency medical condition to the manifestation of "acute symptoms of sufficient severity * * * such that the absence of immediate medical attention could reasonably be expected to result in: (a) Placing the health of the individual * * * in serious jeopardy; (b) serious impairment to bodily functions; [or] (c) serious dysfunction of any bodily organ or part." He suggested that health care professionals will be confused by the different use of the term "emergency" in this regulation and under the Emergency Medical Treatment and Active Labor Act.

The agency disagrees with these comments. Sufficient guidance is given in the regulation in § 50.24, particularly in § 50.24(a)(2)(iii), to ensure that there is a clear understanding of what constitutes a life-threatening situation that could invoke this rule and to ensure that it is not used routinely in all emergency research. In addition, each clinical investigation will be reviewed by FDA and the IRB to help ensure that this exception from informed consent is not used for research for which it was not intended. Further, emergency room personnel should not be confused because they should know when they are participating in FDA regulated research. The agency notes that the purpose of the Emergency Medical Treatment and Active Labor Act is different from this rule. This informed consent exception is intended to allow certain FDA-regulated research to proceed without informed consent provided specific conditions are met. Entities that deal with both regulations

will be able to understand whether one or the other regulation applies.

B. Exception Criteria

1. Section 50.24(a)

27. One comment suggested that additional conditions be added to § 50.24(a) to reinforce the statement in the preamble to the proposed rule that appropriate evidence is available to document clinical equipoise and to ensure that efforts are made to obtain consent from a legally authorized representative whenever possible. The two proposed additional sections would read: "[a]ppropriate animal and preclinical trial studies have been completed, and the information derived from those and related studies support the likelihood of providing a direct benefit to the individual subjects" and "[t]he IRB finds that the researcher defined the length of the therapeutic window based on scientific evidence, will try to contact the legally authorized representative within that window of time, and will ask each representative contacted for consent within that window rather than waive consent. The researcher will track the number of representatives contacted and provide that information to the IRB."

The agency agrees that these are important concepts that should be contained explicitly in the regulation. It has incorporated these comments in the regulation, with slight modification to the language proposed in the comment. The agency has added a new paragraph to § 50.24(a)(3) to read as follows: "(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects." The agency also has added a new paragraph § 50.24(a)(5) and a new paragraph § 50.24(a)(7)(v). The new paragraph § 50.24(a)(5) reads as follows: "(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without informed consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review." The new paragraph § 50.24(a)(7)(v) reads as

follows: "(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review." The agency notes that if the window of time is narrow, it will be difficult or impossible to identify a legally authorized representative or family member, especially for potential subjects whose identities are unknown at the time of presentation.

28. One comment suggested that, in order to prevent abuses, the agency provide all IRB's with standardized forms that strictly define the circumstances and process for an IRB to invoke the waiver of informed consent.

The agency does not think that standardized forms would be useful or practical. The regulation provides sufficient information and allows flexibility for each IRB to develop procedures and methods (and forms, if necessary) to fulfill its requirements.

29. Several wording changes were suggested to clarify § 50.24(a). Two comments suggested that § 50.24(a) be revised to add "prior to initiation of research" after the words "without requiring that informed consent be obtained" in order to stress that consent is being waived for the necessary immediate intervention.

The agency thinks this change is unnecessary. This is clear from § 50.24(a)(2) and new § 50.24(a)(5).

30. One comment suggested the addition "of all research subjects" following the phrase "without requiring that informed consent" and modifying the parenthetical phrase in the next sentence to read: "(with the concurrence of a licensed physician voting member of the IRB or the concurrence of a licensed physician who serves as a consultant)."

The agency has incorporated this language, with minor changes, to emphasize the need for concurrence by a licensed physician who is either an IRB member or consultant and who is not otherwise participating in the clinical investigation. The agency recognizes that in some instances it will be possible to obtain informed consent from some individuals or their legal representatives, or contact a family member when this exception is invoked

for a clinical investigation. The agency has not included the term "voting" because it does not believe that it is necessary to explicitly require that this licensed physician who concurs be a voting member of the IRB because concurrence by this licensed physician is required by the regulation. Since 1981, FDA has stated its expectations that an IRB that reviews investigational new drug studies will include at least one physician. (See 46 FR 8942 at 8966, January 27, 1981.) This expectation is not changed by this rule.

31. Other comments were received on the "concurring licensed physician member or consultant." Three comments felt that this physician member or consultant would add nothing to the process because of pressure to endorse the study; one comment suggested that the interests of subjects would be better served if this physician or consultant were independent of the IRB; two comments suggested that the physician be independent of the investigator (i.e., have no ties to or be in the same department or supervised by, the investigator).

The requirement for a concurring licensed physician is contained in the Medical Device Amendments of 1976 and, thus, it must be retained. The agency agrees with the need for this individual to be independent from the clinical investigation but disagrees with the suggestion that the physician be independent of the IRB. Thus, the agency has amended the language in § 50.24(a) to make clear that the licensed physician must be one who is not otherwise participating in the clinical investigation. This language parallels the language contained in § 50.23(a).

32. One of these comments suggested that an independent ombudsman who is aware of the acute risks of the specific research, the long term risks of the research for the individual, family, and society, based on the condition of the potential subject be appointed to oversee the study.

The agency does not agree. There is no need for a special requirement for an ombudsman for these clinical investigations. Current § 50.25(a)(7) requires the consent form to contain an "explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject." It may be the IRB or some other designated individual who performs these ombudsman-type functions for these investigations.

2. Section 50.24(a)(1)

33. A few comments expressed concern about the phrase contained in § 50.24(a)(1) that "available treatments are unproven or unsatisfactory." One comment suggested that "unproven" be changed to "ineffective."

The agency disagrees with this suggestion because one may have insufficient data to know whether a treatment is ineffective. One may, however, know from the limited data available that it is "unproven."

34. Another comment suggested that the phrase "available treatments are unproven or unsatisfactory" be changed to read "the efficacy of available treatments has not been demonstrated, or is regarded as unsatisfactory."

The agency does not believe this change is necessary or desirable. Available treatments need to be assessed in terms of both safety and effectiveness. The agency believes that the change proposed in the comment focuses solely on effectiveness.

35. Another comment expressed concern that nonscientific members of IRB's will have a particularly difficult time making determinations about whether available treatments are unproven or unsatisfactory.

The agency disagrees. Current § 56.107(a) requires the IRB membership to possess the professional competence necessary to review specific research activities. Further, current § 56.107(f) permits an IRB to invite " * * * individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB." Thus, the IRB should have sufficient information from its own professional expertise, or from consultants, to make determinations about whether available treatments are unproven or unsatisfactory.

36. One comment suggested that guidance on the criteria for determining that current therapy is unsatisfactory should be provided or that the rule should explicitly recognize that IRB's have the discretion to make independent decisions on this point. One comment suggested that a study be allowed to proceed if there is an alternative therapy, provided that equipoise exists between the investigational product and current therapy.

It is clear from the existing wording in § 50.24(a) that it is the IRB's responsibility to make decisions as to whether the criteria in the rule are met. The agency notes that it will also be reviewing these clinical investigations and will evaluate whether these

investigations meet the criteria in this regulation. There is nothing in this rule that would prohibit an investigation from proceeding if there is an alternative therapy where the alternative therapy is unproven or unsatisfactory. The agency expects that in most clinical investigations under this rule, the experimental intervention will be added to standard therapy. That is, subjects in the investigation would receive standard therapy, with a portion of the subjects receiving the investigational product in addition. In some clinical investigations, some subjects may receive standard therapy, while others may receive the investigational product instead of standard therapy because, for example, use of the investigational product precludes use of the standard treatment. In these latter investigations, the IRB may need to look more closely at why standard therapy is unproven or unsatisfactory, and may want to review additional preclinical data or results in less ill human subjects that the intervention is promising, because the standard care will not be provided to a portion of the subject population.

37. Other comments suggested that without clear definitions for "unsatisfactory" and other terms used in the proposal's preamble to describe clinical equipoise, i.e., "unknown," "believe," and "reasonable minority," that abuse of the consent exception is likely.

The agency disagrees with these comments. The agency has explained this provision in more detail in the preamble to the proposed rule and believes that such definitions are unnecessary. The agency also notes that the conduct of this research will be carefully monitored and will be subjected to public scrutiny through the requirements for community consultation and community disclosure. In the preamble to the proposed rule, the agency stated that "[w]hen the relative benefits and risks of the proposed intervention, as compared to standard therapy, are unknown, or thought to be equivalent or better, there is clinical equipoise between the historic intervention and the proposed test intervention. Clinical equipoise would exist * * * whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than, the standard treatment." (60 FR 49086 at 49093, September 21, 1995.) The agency thinks that this description provides sufficient guidance to IRB's and that it is appropriate to allow IRB's to determine when clinical equipoise exists.

38. A number of comments suggested that the scope of the research covered by the proposed rule and contained in § 50.24(a)(1) be extended to conditions beyond those that are immediately life-threatening so that conditions that result in permanent disabilities, such as a long-term or permanent coma, or conditions that would result in other serious irreversible injury are included under the rule. One example given was a near-drowning patient resuscitated in the prehospital setting who arrives at the Emergency Department comatose; the acute injury may no longer be immediately life-threatening, but the chances that the patient will regain consciousness again are highly unlikely. One comment noted that FDA has in the past interpreted "life-threatening" to include threats of serious disability and, if this is intended in the proposed rule, it would be helpful to add this interpretation to the supplementary information. Another comment suggested that both stroke and head injury do not necessarily immediately result in death and that potentially effective treatments are being developed for these conditions which may leave the patient with profound deficits. This comment proposed that such emergencies be covered under the final rule. Two comments suggested that "life-threatening" be defined and limited to include only those situations believed to be immediately life-threatening. Another comment suggested that "emergency privilege" is limited and should extend to care needed to stabilize or prevent further deterioration of the patient's condition as well as care necessary to prevent death or serious bodily injury or harm. Therefore, the care justified must be balanced with the emergent nature of the patient's condition, the patient's potentially transient incompetence to make decisions and give consent, and the time needed to make a reasonable effort to contact and involve the patient's family.

The agency notes that the Medical Device Amendments limit this exception to life-threatening situations; the agency and the IRB will need to judge each clinical investigation to ensure that it meets the criteria of the statute and regulations. Specifically, the IRB must conclude that the intervention to treat a life-threatening condition must be administered before consent can be obtained.

The criteria contained in the rule do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before

consent from a legally authorized representative is feasible. Life-threatening includes diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted. (See § 312.81.) People with the conditions cited in the examples provided in the comments—e.g., long-term or permanent coma, stroke and head injury—may survive for long periods but the likelihood of survival is not known during the therapeutic window of treatment. People with these conditions are clearly at increased risk of death due to infection, pulmonary embolism, progression of disease, etc. The rule would apply in such situations if the intervention must be given before consent is feasible in order to be successful. The informed consent waiver provision is not intended to apply to persons who are not in an emergent situation, e.g., individuals who have been in a coma for a long period of time and for whom the research intervention should await the availability of a legally authorized representative of the subject.

39. The agency received a number of comments on the reference to placebo-controlled trials in § 50.24(a)(1). One comment stated that it was vitally important to retain the reference. Other comments requested that the reference be removed. Reasons given for its removal included concern that placebo-controlled studies will not meet the requirement of clinical equipoise unless the placebo control is the standard of care for the situation or there is absolutely no standard therapy; that this conflicts with agency statements that the use of a placebo is not necessary when the end-point is clear and reasonably predictable; it is inappropriate for the agency to specify one study-design among many; and that unless the potential subject or legally authorized representative can consent, a placebo should not be an alternative.

Some of the comments appear to presume that in a placebo-controlled trial, the placebo group would be untreated. In virtually all cases, when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, the test treatment or a placebo. An exception to this would be the situation in which the test is to determine whether standard treatment is in fact useful. In that case, there must be a group that does not receive it. The agency believes that it is important to recognize in the regulation that placebo-controlled trials may be conducted under this emergency research provision; thus, it is retaining the

wording in this section. Different kinds of controls are described in FDA's regulations. For example, FDA regulations for drugs (§ 314.126) describe five kinds of study designs that can be used in carrying out the well-controlled investigations needed under law to provide the "substantial evidence of effectiveness" needed to market a drug. They are: Placebo concurrent control, dose-response concurrent control, no-treatment concurrent control, active treatment concurrent control, and historical control. In any given year, drug approvals will be based on clinical investigations using each of these designs. The study design used must, however, be adequate to the task of providing evidence that the drug or device will have the effect claimed.

40. Two comments suggested changing the wording of § 50.24(a)(1) from "what particular intervention is most beneficial" to "the safety and efficacy of a particular intervention" in order to provide greater flexibility. Another comment suggested that "most beneficial" be followed by the clarifying phrase "to patients in the life-threatening situation."

The agency agrees that it would be more precise to indicate that the clinical investigation is necessary to determine whether a particular intervention is safe and effective and it has modified the wording in the regulation accordingly.

3. Section 50.24(a)(2)

41. A number of comments on § 50.24(a)(2)(ii) recommended that "or family members" be added to "legally authorized representatives" at each occurrence in the proposal and in its conforming amendments in order to ensure that the exception is used only in those cases where it is not feasible to contact the legally authorized representative or a family member.

The agency generally agrees with these comments for the reasons previously stated and has modified the regulations accordingly.

42. Two comments requested that a definition of the term "legally authorized representative" be provided. One comment suggested that the language be clarified to read " * * * consent from the subjects' legally authorized representatives is feasible."

"Legally authorized representative" is currently defined in § 50.3(m) to mean "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." This definition is being retained in the regulation. The agency has added the clarifying language that it

is "the subject's" legally authorized representative.

43. One comment questioned whether one should seek oral consent/assent from a family member or other individual in those instances in which there may only be a few moments to convey the nature of the intervention, precluding full informed consent. If such assent is not given, the comment requested clarification on options available to the researcher.

If it is feasible to obtain informed consent for some potential subjects, informed consent is required for those individuals. If there is insufficient time to obtain informed consent for some potential subjects, but there is sufficient time to convey some basic risk and benefit information about the clinical investigation, then that information should be provided to the subject, the subject's legally authorized representative, or the subject's family member. If the subject, legally authorized representative, or family member objects to the individual's inclusion in the investigation based upon the information provided, then that individual should be excluded from participation in the clinical investigation. If only partial information was conveyed, then the information described in § 50.24(b) is to be provided at the earliest feasible opportunity.

44. Another comment suggested that there be a requirement that the determination that a subject cannot provide informed consent and efforts made to obtain informed consent from the subject's legally authorized representative be documented and notarized by an individual not directly involved in the research. This comment suggested that without such a requirement, investigators are likely to make little effort to obtain consent from subjects prior to enrollment. This concern was echoed by another comment, which suggested that the investigators' documentation of efforts to obtain informed consent would encourage researchers to expend greater efforts to obtain informed consent for these activities. Another comment suggested that this documentation be made by an individual not affiliated with the study team.

The agency expects the IRB to determine, based on the specific details of the individual clinical investigation (including the window of opportunity for treatment), the procedures the investigator must follow to attempt to obtain informed consent before enrolling a subject in an investigation without such consent. The agency has added a new paragraph § 50.24(a)(5) that requires the investigator to attempt to

contact a legally authorized representative for each subject within the therapeutic window and, if feasible, ask for consent within that window rather than proceeding without consent. The agency also has added a new paragraph § 50.24(a)(7)(v) that requires the investigator to attempt to contact a family member within the therapeutic window and ask whether the family member objects to the subject's participation in the clinical investigation, if informed consent is not feasible and a legally authorized representative is not available. IRB's may create a hierarchy of family members or impose other conditions to increase the protections provided to research subjects. These paragraphs further require the investigator to summarize efforts made to contact representatives and family members and to make this information available to the IRB at the time of continuing review. The agency believes that these procedures will ensure that appropriate efforts are made by the investigator to obtain consent from subjects prior to enrollment. The agency expects these procedures to be documented in the protocol and/or by the IRB, and the efforts made by investigators to be documented in the material presented to the IRB for its continuing review. The agency believes that this documentation provides the necessary protections suggested by these comments.

45. One comment suggested that § 50.24(a)(2)(iii) be modified to read "There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research study," omitting the remainder of the sentence.

The agency agrees that the last phrase in the proposal that read "because the emergence of the condition to be studied cannot be predicted reliably in particular individuals" is not needed and it has therefore deleted this phrase from the final rule as suggested.

46. Although two comments stressed the importance of retaining the word "reasonable" in order to allow IRB's to exercise the judgment necessary to make satisfactory decisions about application of the exception in particular contexts, another comment suggested that the term "reasonable" may provide more flexibility than is desirable.

The agency thinks that IRB's must be allowed to make responsible judgments when they review clinical investigations, and that it is important to retain the term "reasonable" in order to permit the IRB to judge the particular circumstances surrounding each investigation under review.

47. One comment asked how to document the case where prospective individuals have been notified and prior consent for participation has been sought in an institution with several co-investigators or where more than one institution in the area may be participating in the research. The comment asked further whether only those subjects with the condition who gave prior consent could be enrolled and whether those who did not render a decision would be excluded from participation in the study.

Generally, the agency recommends that when prospective consent is being sought in an institution, the documentation that a potential subject consented or refused to consent be placed prominently in the subject's medical file. Consent will typically be documented through a signature on the consent form. It is the responsibility of the clinical investigator to determine how to identify prospective subjects who have agreed or refused to participate in a clinical investigation if they should become eligible in order to help ensure that their decisions are followed. When an IRB determines that it is not appropriate to waive the requirement of informed consent because there is a reasonable way to identify prospectively the individuals likely to become eligible for the clinical investigation, then only those subjects with the condition who gave prior consent may be enrolled in the investigation. Those individuals who either did not make a decision or who refused would be excluded from participation in the investigation.

48. Another comment noted that if a subset of the general population can be identified as potential subjects, anticipatory informed consent must be obtained, even if the subset is a very small percentage of a large patient population. For example, where a small percentage of patients undergoing a standard procedure may suffer a complication that would render them unconscious and make them potential subjects, informed consent should be obtained for that clinical investigation. The comment went on to note that if that procedure carries some known risk for a complication, the potential subjects would need to be informed of that risk in any event, and obtaining anticipatory consent for the investigation should therefore not be burdensome.

The agency generally agrees with the concept that obtaining anticipatory consent from a target population where the complication rate is modest often would be feasible. As the complication rate grows small and the population

hard to identify, this strategy becomes problematic. Each clinical investigation must be judged individually by FDA and the IRB.

49. Another comment suggested that the Coalition Conference Consensus Statement wrongly discounted the value of securing and the ability to secure prospective consent from identifiable individuals at high risk for study enrollment, particularly those in hospitals, and that neither the consensus statement nor the proposed rule mentioned the role of advance medical directives in guiding enrollment decisions. This comment, supported by others, suggested that a good faith effort should be mandated to locate advance directives and that the regulation should include a new paragraph, as follows: "Any individual likely to be eligible for a research protocol under this section may not be enrolled in the research if the investigators know, or reasonably should know, that the individual did not want to receive medical interventions of the type under study." Another comment suggested that, although advance directives have been addressed in clinical practice, their application to the conduct of clinical research has not received much scrutiny. This comment described the difficult task for potential subjects to imagine the kind of research they would want should they suffer a catastrophic illness; it went on to recommend that either FDA clarify how it intends clinical investigators to adopt the practice of advance consent, or this statement should be deleted. It further suggested that FDA consider requiring the use of consent auditors whose role would be to determine whether the subject truly understands the consent process.

The agency does not believe that these comments require a change in this regulation. The agency recognizes that it may be possible in some situations to secure prospective consent from identifiable individuals at high risk for study enrollment, particularly if they are inpatients. It is for that reason that the agency has included § 50.24(a)(2)(iii), which requires the IRB to determine that there is no reasonable way to identify prospectively the individuals likely to become eligible for the clinical investigation. Both the American Hospital Association's Patient Bill of Rights and section 4206 of the Omnibus Budget Reconciliation Act of 1990 recognize a patient's right to participate in and direct health care decisions affecting the patient. The agency agrees, particularly for clinical investigations involving inpatients, that

appropriate efforts be made to review the patient's medical file to determine whether there exists an advance medical directive or other indication of the patient's desires (e.g., do not resuscitate order). However, the agency also recognizes that, for at least some of the research that will be eligible for this exemption, there will be insufficient time to search for or locate such directives. The IRB should be knowledgeable about an institution's procedures regarding the use of advance medical directives and assess whether the proposed clinical investigation is consistent with those procedures.

As discussed previously, if an IRB determines that it is not appropriate to waive the requirement of informed consent because there is a reasonable way to identify prospectively the individuals likely to become eligible for the clinical investigation, then only those subjects with the condition who gave prior consent may be enrolled in the investigation. Those individuals who either did not make a decision or who refused would be excluded from participation in the investigation. For research where individuals can give informed consent prospectively, the individual's consent or refusal should be documented in such a way to ensure that the individual's determinations are followed. As in other research that is reviewed by an IRB, it is up to the IRB to determine whether there is a need for a consent auditor.

50. Another comment recommended that the question of whether prior consent of subjects must be obtained should be resolved by considering the following questions: (1) From which populations will subjects be drawn; (2) what is the probability that any particular member of the at-risk population will become a potential subject; (3) where is the population from which subjects will be drawn; (4) how much effort is needed to inform the population of the study; and (5) what is the most effective communications media or mechanism to reach the population. Based on these questions, this comment recommended that a new section be added that would state: "When individuals likely to become eligible for the research are members of identifiable and accessible populations of the community at large, reasonable effort to target communications to those sub-populations should be made."

This comment suggests what may be a reasonable thought process for an IRB to follow. However, it combines two different concepts: communication with the community and prior consent of individual subjects. As the agency has previously stated, if one can obtain prior

consent of subjects, that should be done. Examples of situations where it may be feasible to obtain prior informed consent include: use of a surgical procedure with a known severe consequence; administration of a drug product with a known serious adverse reaction; identification of a population with a particular disease or condition who are at an extremely high risk for a serious event. In each of these instances, it may be feasible to identify in advance the specific patient population susceptible to the condition being studied and obtain consent. The agency believes that it would be inappropriate to add the suggested section to the regulation because it confuses efforts to inform the community with efforts to obtain prior consent of the individual.

51. Another comment recommended that the agency require preliminary studies of new products in patients admitted to intensive or critical care units who are able to consent or who have a legal representative who can consent on their behalf. This comment suggested that this would strengthen an inadequacy in the existing regulations that permits studies (with subjects unable to provide informed consent) to begin, without any knowledge regarding the clinical performance of the drug/device.

Given the nature of the product and the medical condition, this suggestion may not be feasible for many of these clinical investigations. The agency, in its review of these investigations, will review the adequacy of the information about the proposed intervention to help ensure that there is sufficient knowledge, including clinical performance in other settings when possible, of the drug or device to justify its use in such investigations. In addition, the regulation has been modified to specify that evidence from appropriate animal and other preclinical studies support the potential for the intervention to provide a direct benefit to the individual subjects.

4. Section 50.24(a)(3)

52. A number of comments suggested deleting the phrase "is in the interests of the subjects" in § 50.24(a)(3) in part because this phrase requires that a judgment be made about subjects whose interests may be largely, if not totally, unknown to the IRB and to the investigators. Some comments argued that there would be no possible benefit to the subject, but only to society at large if the experimental intervention were shown to be effective; the goal of the research is not to benefit subjects in the research, but rather to benefit science in the pursuit of knowledge.

Others suggested that § 50.24(a)(3) be modified to read: "The opportunity to participate in the research holds out the prospect of direct benefit to the subjects because * * *." Other comments objected to the word "opportunity" as being disingenuous and paternalistic and suggested that this section be modified to read: "Participation in the research * * *."

The agency agrees that § 50.24(a)(3) should be modified in response to some of these comments. The first comment points out that one cannot really know about all the interests of a person in these situations. The modification would make clear that the clinical investigation holds out the prospect of direct benefit to the subjects. The agency does not agree with the second comment that there would be no possible benefit to the subject, but only to society at large. To justify the use of this exception the IRB must believe that participation in the study holds out the prospect of direct benefit to the subjects. It is also true, but not the basis for the exception, that the interests of society will be served by the waiver because the research will produce valuable knowledge, applicable to future patients, that would otherwise never be obtained; an IRB should not approve a clinical investigation that is poorly designed and, thus, unable to answer the scientific question posed. In response to the third suggestion, the agency is clarifying any mis-impression that it would be the "opportunity" rather than the actual "participation" in the research that is beneficial. The agency intended that participation in the research should hold out the prospect of direct benefit to the subject and has revised the rule accordingly.

53. Another comment noted that if the null hypothesis is plausible, that is, if the effect of the investigational intervention is no different from that of the standard treatment, the subject has little to gain by being in a randomized trial rather than being treated by whichever arm of the study is standard. This comment recommended that historical controls be used when investigators or potential subjects are not "indifferent" to the treatment alternatives.

If the use of a historical control is appropriate for the clinical situation being studied, that control may be used, but the difficulties of this design are well-known and it cannot reliably assess small, but potentially meaningful benefits and is frequently associated with false positive results. The comment related to the null hypothesis is not unique to emergency research. Rather, it reflects a fundamental ethical dilemma

in all clinical trials. This dilemma, however, has not been considered by most bioethicists as an impassable obstacle for the conduct of controlled trials. This is because continuing an intervention, even one thought to have promise, without determining that it does provide benefit, is not a responsible alternative. The investigational intervention in these clinical investigations must be promising, but one does not know that it is in fact safe and effective. Further, in these investigations, the standard treatment being compared to the investigational product or to which the investigational product is added will be of unproven benefit or unsatisfactory.

54. One comment suggested that an additional condition be added to 50.24(a)(3) which would require that the weight of scientific evidence be sufficient to support the likelihood that the individual subjects will receive a direct benefit. Another comment suggested that the rule require a progression of research from less severe medical cases to more severe and only permit the inclusion of patients unable to consent if there is an ombudsman independent from the research activity.

As previously described, FDA has added a new § 50.24(a)(3)(ii) which requires that "Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects." There is nothing in this rule that would preclude research from being conducted in subjects with less severe medical conditions (not in a life-threatening situation) before being conducted in subjects with more severe medical conditions provided that informed consent is obtained from the research subjects with the less severe conditions. When this exception is invoked for a particular clinical investigation, however, the FDA, sponsor, clinical investigator, and IRB will be responsible for ensuring that the subject population is appropriate; that is, that the subjects are in a life-threatening situation.

55. One comment recommended that § 50.24(a)(3)(i) be reworded to clarify that "subjects are facing a life-threatening situation that necessitates intervention."

The agency agrees with the comment and has modified this section accordingly.

56. One comment suggested that proposed § 50.24(a)(3)(ii) be reworded to clarify that the rule is addressing the "prospective subjects' condition" and that "current therapy" equates to

"standard therapy." This comment suggested that proposed § 50.24(a)(3)(ii) be rewritten to state "risks associated with the intervention are reasonable in the light of what is known of the prospective subjects' medical condition, the risks and benefits of standard therapy * * *."

The agency has renumbered proposed § 50.24(a)(3)(ii) to be § 50.24(a)(3)(iii) in the final rule. The agency agrees with the comment and has modified this section accordingly. The risk and benefit assessment that is required by § 50.24(a)(3)(iii) will be conducted for future subjects meeting the entry criteria for the clinical investigation; therefore, it is appropriate to refer to these subjects as the "potential class of subjects." The agency intended that the risks and benefits of "standard" therapy be considered; it recognizes that "current" therapy may be too broad.

57. Several comments requested a definition of "reasonable." One comment noted that the rule requires a complex judgment about risks and benefits and yet lacks specificity as to how this judgment is to be made. This comment noted that in most research, an IRB can rely on the risks and benefits being explained to the subject and the subject judging whether they are reasonable. In the case of the research covered by this regulation, that recourse is not available.

It is not possible to be specific about how to make the judgment about risks and benefits because, as the comment notes, the judgment to be made is complex, with different information and considerations determined by the particular clinical investigation. The agency thinks that sufficient clarity is contained in § 50.24(a)(3)(iii) to allow an IRB to understand that it must consider: (1) What is known about the medical condition, (2) what is known about standard therapy, and (3) what is known about the proposed intervention or activity. The risks of the investigation must be considered reasonable in relationship to all of this information. The agency does not think that this requirement needs further explanation.

58. Two comments suggested that proposed § 50.24(a)(3)(ii) be modified to incorporate the Coalition of Acute Resuscitation and Critical Care Researcher's concept of "appropriate incremental risk" stating that this would better protect the rights of subjects. One of these comments suggested that the 1981 FDA regulatory requirement that "there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the

life of the subject" is the standard that should be used in this regulation.

The agency disagrees with both suggestions. The protections provided by the rule are substantial and sufficient without these changes. The standard for risks, described in the regulation, are that they be "reasonable" in relationship to what is known of the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any; and what is known about the risks and benefits of the proposed intervention. The term "appropriate incremental risk" does not have a clearly different meaning, although it may imply greater precision than usually exists. In order to invoke this exception, the available treatments must be unproven or be regarded as unsatisfactory.

5. Section 50.24(a)(4)

59. Several comments suggested deleting or clarifying § 50.24(a)(4) concerning the "practicability" of conducting the research without the waiver. One comment requested clarification as to whether "practicability" only referred to whether there is sufficient time to obtain consent from a subject's legally authorized representative; and recommended that if this is the sole basis for determining practicability, it should be added to the regulation. Another comment noted that "practicability" should not refer to convenience, cost, or speed. One other individual commented that although certain institutions may be unable to perform specific acute injury research because of logistical considerations, it is likely that most research projects could be designed such that performance under existing rules for nonconsenting subjects would be possible in other locations. This comment cited a multicenter trial where only one institution requested a waiver.

One comment suggested that § 50.24(a)(2)(ii) is sufficient for determining whether a study can be done; this comment stated that the primary reason that it would not be practical to carry out the research without the waiver would be because it is not feasible to contact the legally authorized representative or family member before the intervention must be administered.

Another comment objected to § 50.24(a)(4) and argued that the rule should state that if there are any potential subjects otherwise eligible for a trial for whom consent from a legally authorized representative cannot be obtained, the provisions of § 50.24(a) may be utilized to include them, even if the trial could be carried out without

their participation, so long as all of the requirements for that section are met. This comment noted that if this section meant only that consent should be obtained wherever it can be, even when most subjects in a study do not have an available legally authorized representative, it would be unexceptionable, but the section goes beyond that to proscribe participation in a trial by patients without consent when the majority of eligible patients do have such consent available because in that case the study can be carried out "practically" without those patients. This comment noted that it is the value of participation to the subject that permits an exception to the informed consent requirement; that implicit in the proposal is the view that most patients would choose a chance to receive promising rather than standard therapy that is known to have an often unsatisfactory outcome. Thus, to exclude patients unable to consent from this research is unethical, even if the study could be conducted with subjects for whom surrogate consent is possible.

The agency has carefully considered these comments, particularly the latter comment that in effect contended that the "practically" requirement is inconsistent with the ethical basis for the rule because it implies that the exception to consent is available to serve the community's needs rather than the individual's. The agency included this requirement not because it thought the research was not in individual patients' interests, but because research without informed consent represents a more difficult and complex situation than research with consent, in that it is a kind of research with greater than usual ethical issues that should be taken only when necessary. This is because the agency believes it is generally preferable to obtain case-by-case consent even from a representative of the individual. Just as consent by the subject is preferable to consent by their representative, consent by the subject's representative is preferable to the procedure in this regulation. This does not mean that these procedures are inadequate or unethical; rather, it recognizes within the realm of ethically proper actions a hierarchy of values and that we should seek the highest level of those values feasible in this situation.

Similar considerations have arisen in the past. The National Commission for the Protection of Research Subjects of Biomedical and Behavioral Research argued that (wherever possible) clinical trials intended to benefit young children should first involve adult subjects, later older children as subjects, and finally trials in younger children (who cannot

consent or assent). This is not because the trials in younger subjects are considered inappropriate or ethically doubtful. The agency understands the Commission to be saying that the principle of respect for persons of diminished autonomy applies in such a way that the less autonomy a subject possesses, the less suitable that subject is for research, even if the research shows promise. The Commission did not say to never involve persons with minimal or no capacity to exercise autonomy, but to do so only as a last resort.

It is critical to recognize that an investigation of a promising (but unproven) intervention is not carried out universally, i.e., studies are conducted in particular places. Similarly, although a parent of a young child could argue that his or her child should not have to wait for the trial in adults and older children to be completed before having an opportunity to participate in research, the Commission was not persuaded by that argument (although, in some cases, early trials in young children might be carried out). The Commission did not recognize the right of a needy person to gain access to a research protocol. In choosing among sites for a clinical investigation, for example, it is usual to select those in which the skills of investigators and availability of subjects appear to predict an ability to carry out the investigation successfully. Similarly, it is reasonable to consider, in deciding where or in whom to conduct an investigation, the ability of subjects to consent (or have consent given for them). Widely accepted ethical principles indicate that a decision to participate or not to participate in an investigation should, if at all possible, be made by a competent subject who should (as stated in the Nuremberg Code) be free of all force, fraud, fear, or coercion. An exception from the requirement for informed consent should be rare and narrow, confined to cases where consenting subjects are not reasonably available. In addition, participation in the research must hold out the prospect of direct benefit to the subjects and the investigation must be one that is capable of providing useful scientific/medical information.

If serving the interests of the subjects were considered sufficient alone, that would imply that potential subjects have a right to participate in the trial, an inappropriate consideration for an investigational use and unrealistic, because studies cannot in fact be carried out at all potential sites and in all patients.

The agency thus agrees with the comment that it is necessary for there to be value to the subject from participating in the research; but, given the general principle of obtaining informed consent where possible, does not think that such potential benefit is sufficient justification to include nonconsenting patients when it is reasonably possible to conduct the clinical investigation in subjects who can consent.

Therefore, if scientifically sound research can be practicably carried out using only consenting subjects (directly, or in most cases for the research contemplated in the rule, with legally authorized representatives), then the agency thinks it should be carried out without involving nonconsenting subjects. By practicable, the agency means, for example, (1) That recruitment of consenting subjects does not bias the science and the science is no less rigorous as a result of restricting it to consenting subjects; or (2) that the research is not unduly delayed by restricting it to consenting subjects.

6. Section 50.24(a)(5)(i)-(a)(5)(iii)—Community Consultation and Public Disclosure

The greatest number of comments were received on § 50.24(a)(5)(i) through (a)(5)(iii), which have been renumbered § 50.24(a)(7)(i) through (a)(7)(iii) in this final rule in order to have a more logical presentation of information. To assist readers, these sections will be referred to as § 50.24(a)(7)(i) through (iii) in the discussion that follows. While most comments supported the requirement for community consultation and public disclosure, many requested clarification, offered suggestions, or concluded that fulfilling these requirements would be impossible. Other comments questioned whose responsibility it would be to disclose—the clinical investigator, sponsor, or IRB. These comments are discussed in more detail below.

60. A number of comments suggested alternatives to the requirement for § 50.24(a)(7)(i) for consultation with representatives of the communities from which the subjects will be drawn. These included limiting this provision to only those diseases for which a patient advocacy organization exists; relying on the existing IRB mechanism that already requires inclusion of an individual not otherwise affiliated with the institution; requiring that IRB's have a community member or an ad hoc community consultant who is intimately involved with the projected research population; permitting an IRB to determine that balanced community consultation is not feasible and documenting and reporting

this determination to the sponsor and to FDA; increasing public participation in the IRB process by specifying acceptable kinds of individuals (e.g., clergy, local commissioners, police, paramedics) who should be added to the IRB (limited to two); having the IRB membership include individuals from the community groups from which subjects would come and ensuring that the preferences of those members were followed; establishing a standing community advisory board that would reflect the diverse values and beliefs of the community. This board could serve several IRB's within the same community. Another comment stressed that the IRB must take into account the diverse religious and community beliefs and attitudes about treatment of the dying and of research.

None of the suggested alternatives to § 50.24(a)(7)(i) would by themselves provide the protections of broad community consultation of this section. While an IRB may appropriately decide to supplement its members with consultants from the community, broader consultation with the community is needed for this type of research. The agency expects the IRB to provide an opportunity for the community from which research subjects may be drawn to understand the proposed clinical investigation and its risks and benefits and to discuss the investigation. The IRB should consider this community discussion in reviewing the investigation. Based on this community consultation, the IRB may decide, among other things, that it is appropriate to attempt to exclude certain groups from participation in the investigation; or that wider community consultation and discussion is needed. As described in the preamble to the proposed rule (60 FR 49086, September 21, 1995), IRB's should consider, for example, having a public meeting in the community to discuss the protocol; establishing a separate panel of members of the community from which the subjects will be drawn; including consultants to the IRB from the community from which the subjects will be drawn; enhancing the membership of the IRB by adding members who are not affiliated with the institution and are representative of the community; or developing other mechanisms to ensure community involvement and input into the IRB's decisionmaking process. It is likely that multiple methods may be needed in order to provide the supplemental information that the IRB will need from the community to review this research.

61. Another comment noted that tribal approval and not just consultation

should be required and suggested that for American Indian/Alaska Native tribal governments, the regulation require approval by the tribal government for all research done within its jurisdiction. This comment suggested that the regulation permit a recognized government of the political community to disapprove research.

This regulation does not restrict or have an impact on any existing authority of tribal governments to review and approve or disapprove research that would otherwise be conducted on persons residing in tribal jurisdictional boundaries. If existing tribal authorities require tribal government approval of such research before it proceeds, then the tribal governments continue to have that authority. Thus, the agency thinks that adopting this suggestion is unnecessary.

62. Comments opposed to the community consultation required in § 50.24(a)(7)(i) suggested that the current requirement for a community representative on the IRB (56.107(a)) was adequate; that this would be burdensome for noncommercially sponsored studies; that it was an insurmountable goal and that there is no guarantee that an IRB could reach all impacted individuals. Other comments suggested that only a central agency such as FDA or the Public Health Service should decide because the clinical investigator will bias the outreach meetings to a disinterested community that would be unable to make knowledgeable decisions, and the community will be biased because the research would bring funding support to the community, and because it is difficult to define the community, especially for those institutions that receive patients from a large region or State. A number of comments suggested that community consultation could lead to IRB liability on the basis of failure to solicit adequate community participation in the decision process. Other comments noted that disclosure to the community does not substitute for consent and that unless one included information about the subject's right to refuse and how to exercise that right, community consultation would be inadequate.

As discussed previously, the agency does not think that the current IRB membership requirements adequately substitute for the community consultation called for in this rule. The agency thinks that community consultation provides a very important protection for research subjects and, therefore, every effort should be made by the IRB to involve, and consult with,

the community from which research subjects may be drawn.

63. Other comments stated that without clear definition of terms, the vagueness of the requirement would lead to inadequate consultation and disclosure. Another comment noted that if minority or lower income populations were unlikely to agree to the research and they represented a large proportion of the potential research population, then the conduct of the research would violate the principle of justice because these populations would not share in its benefits or burdens.

The agency thinks that IRB's will ensure, through their review and oversight activities, adequate consultation and disclosure. It is impossible, without prescription, to ensure that each subpopulation shares both the benefits or burdens of all research. Achieving the principle of justice is a goal that must be balanced by other principles. In the case of a population that is unwilling to agree to participation in a research activity, honoring this population's unwillingness is, in effect, permitting the community to express its views.

64. A number of comments requested clarification of this requirement. These comments asked how the consultation should take place (newspaper, institutional newsletter, advertisement, local radio stations, meeting); who in the community needs to be informed and who may be legitimate representatives of the community; what the IRB does with the community response (e.g., can a community veto research, what if a small or a large number oppose the research, what is the sponsor or IRB's responsibility to respond to questions or requested changes in the research); how is an IRB to assess the effectiveness of the consultation (e.g., if there is a poor turnout at an adequately publicized meeting, is the IRB obliged to do more)? Another comment requested clarification of what the public representatives and representatives of the population at risk would be asked to do. One comment urged the agency to refrain from providing precise definitions for the various terms in § 50.24(a)(7)(i) through (a)(7)(iii) in order to permit IRB's adequate flexibility in making judgments.

Community consultation is likely to be multifaceted and to use a number of the mechanisms suggested by the comments. As described earlier, the IRB needs to provide an opportunity for broad community discussion. If, for example, there is poor turn-out at a meeting to discuss the research, an IRB may consider targeting specific

community representatives for inclusion in an additional meeting, or it may decide that the research was not found by the community to be objectionable. The IRB is responsible for listening and considering the community's support, concerns, etc., and then ultimately deciding whether the investigation should be modified, approved, or disapproved. The community is expected to provide input to the IRB on its support for or concerns about the research activity.

65. A number of comments requested clarification on who is responsible for the community consultation and disclosure requirements contained in § 50.24(a)(7)(i) through (a)(7)(iii). Most comments suggested that the IRB should be responsible for reviewing and approving the content and method of consultation and disclosure; the sponsor should be responsible for developing the plan for consultation with the community and for disclosure and provide this information to the IRB to review for adequacy.

Although a sponsor may provide to an IRB model information for use in consultation with the community and for disclosure, just as it may now provide a model consent form for a clinical investigation, it is the responsibility of the IRB to ensure the adequacy of the community consultation and disclosure requirements contained in § 50.24(a)(7)(i) and (a)(7)(ii).

66. Another comment recommended that the sponsor and clinical investigator should pay for the costs associated with the disclosure requirements.

The agency does not dictate the entity responsible for the costs related to research. However, the agency anticipates that the sponsor would normally incur the costs associated with disclosure to and consultation with the community.

67. Several comments on § 50.24(a)(7)(ii) suggested that for multicenter trials, disclosure be required once for each metropolitan area and that the disclosure be made by the sponsor or a designated institution in a notice that would list all institutions, investigators, and IRB contacts.

The agency would not object to such centralized disclosure if all of the responsible IRB's agreed that this is appropriate and acceptable.

68. Another comment suggested that instead of requiring disclosure prior to the commencement of the study, disclosure occur at periodic time intervals (e.g., every 2 years) and include a public notice of general

issues, specific projects, results of the research, and permit public input.

It is the responsibility of the IRB to consider how to maintain the flow of information to the community. In addition to requiring disclosure to the community prior to the initiation of the clinical investigation, the IRB may determine that it is appropriate to require further disclosure at periodic intervals of time.

69. Another comment requested that the regulation specifically ban "general disinformation campaigns" by sponsors performing the research.

The agency thinks that such a ban is unnecessary and that IRB involvement in the disclosure process helps to eliminate the possibility that biased or misleading information will be disseminated. The information disseminated will be reviewed by the IRB to ensure its adequacy and balance.

70. A number of comments were opposed to the requirements for disclosure contained in § 50.24(a)(7)(ii). The comments suggested that they would take an exhaustive amount of time; could prevent valuable research because the investigator and institution could be targets of a poorly informed community; the investigator may not be the best individual to discuss the study; they could cause persons to not seek care; they would be burdensome for noncommercially sponsored studies; for parties with an interest in the research, a requirement for disclosure could lead to either a dishonest or incomplete disclosure of information; the regulation requires disclosure of less information than that which would be given to a research subject; that it is essential to include information about financial and economic incentives for the research; and that it is essential to permit public participation in the disclosure sessions.

As discussed previously, it is the IRB's responsibility to determine the information to be disclosed. As described in the preamble to the proposed rule, the IRB should consider how best to publicly disclose, prior to the commencement of the clinical investigation, sufficient information to describe the investigation's risks and benefits, e.g., relevant information from the investigator's brochure, the informed consent document, and investigational protocol. Initial disclosure of information will occur during the community consultation process. Disclosure of this information to the community will inform individuals within the community about the clinical investigation and permit them to raise concerns and objections.

71. Another comment suggested that the release of confidential information required by this section could serve as a disincentive for sponsors to conduct the research and that it would create a precedent that could affect companies not otherwise affected by the regulation.

The agency disagrees with this comment. While it is true that much information relating to clinical investigations is normally treated as confidential by sponsors, the agency believes that when a sponsor chooses to invoke the exception from informed consent contained in this rule that it is essential that reasonable disclosure occur to the community. The agency believes that the benefit to a sponsor of invoking the rule will outweigh concerns that a sponsor will have about disclosing information about the investigation. Because this disclosure is made only when the exception from informed consent is invoked, it will not create any precedent for companies not invoking the exception.

The agency notes that sponsors release research information to investigators and IRB's (for example, through the protocol and investigators brochure) and to potential subjects in the research through the informed consent process and informed consent form; this rule states that the same information should be released to the community so it can be informed as it considers the research.

FDA believes that American Indian and Alaska Native Tribal governments and communities currently require both presentation of the research protocol and reporting results to the community before they permit any research to occur on their reservation. Recent Phase 2 and Phase 3 trials of several vaccines (e.g., Haemophilus B, Hepatitis A, and rotavirus vaccines) have been done on reservations under those rules by the pharmaceutical companies sponsoring the research. Under this rule, no company is required to release additional information to a community if it does not want to have a waiver of consent for its emergency research.

72. One of these comments stated that information is a property right and to require that it be surrendered without compensation may violate the Fifth Amendment of the Constitution.

The agency disagrees with this comment. The Fifth Amendment requires that no private property be taken for a public purpose without just compensation. (U.S. Constitution, Amendment V.) One factor used to determine whether there has been a taking is whether the action interferes with the reasonable investment backed expectations of the owner of the alleged

property right. (*Kaiser Aetna v. United States*, 444 U.S. 164, 175 (1979).) Where a voluntary submitter of information is aware of the conditions under which the information must be disclosed, the submitter gains an economic advantage related to the submission (such as registration), and the disclosure is rationally related to a legitimate government interest, there is no taking. (*Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1007-8 (1984).) Under this rule, the disclosure is directly related to protecting the individual members of a community that may be involved in the clinical investigation without informed consent by providing the community with advance notice of the nature of the investigation and the possibility that they may be involved in the clinical investigation without their informed consent. Furthermore, the regulation provides a mechanism under which the sponsor may perform the clinical investigations and sets the conditions under which the disclosure will occur. Therefore, the regulation serves as advance notice that prevents a sponsor from having any reasonable investment-backed expectation concerning the information and, thus, there is no unconstitutional taking.

73. A number of comments raised questions about § 50.24(a)(7)(ii) including: what criteria would be used to determine that disclosure was adequate; when is the disclosed information to be provided to FDA; what is meant by "sufficient" and "relevant"; whether it is sufficient prior to the study to simply post a notice on the bulletin board; who determines the adequacy of the disclosure; whether this places an obligation to "disclose" or to "disseminate" information to the community; what this disclosure is supposed to accomplish. Clarification was requested as to the method and scope of disclosure.

It is the responsibility of the IRB to determine the "sufficiency" of the information to be disclosed. The agency advises that this information could include, but may not necessarily be limited to, the information that is found in the informed consent document, the investigator's brochure, and the research protocol. The obligation to disclose information includes an obligation to disseminate information to the community. The purposes of disclosure are to provide community confidence in the role of the IRB and in its decisionmaking capability, to permit the community to express its concerns and possible objections to the research, and to inform the community so that it is aware that the research is to be

conducted involving individuals from the community.

74. Another comment suggested that FDA and DHHS should provide IRB's with copies of disclosure forms.

The agency disagrees. It is the IRB's responsibility to determine the method for disclosure and information to be disclosed. A "form" would stifle IRB creativity and flexibility.

75. Comments on § 50.24(a)(7)(iii) suggested that the regulation specifically include the requirement that the underlying data be disclosed following the end of the study; another suggested that product approval decisions should be based on compliance with this requirement as well as the timeliness of disclosure.

The agency does not think that these comments require a change in the regulation. The agency thinks that it is necessary to provide comprehensive summary data from the completed trial to the research community in order to permit other researchers to assess the results of the clinical investigation. The agency thinks that there must be a scientific need to conduct clinical investigations involving subjects who are unable to consent; if previous investigations have already provided the scientific answer, this should be shared broadly with the research community. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, it may need to be supplemented by additional information. The agency has modified § 50.24(a)(7)(iii) to clarify that the information to be disclosed is to include the demographic characteristics (age, gender, and race) of the research population.

In response to the suggestion that product approval decisions should be based on compliance with this requirement, the agency notes that it has a variety of compliance procedures that it may use to enforce this disclosure requirement.

76. Comments opposed to this disclosure requirement suggested that it would jeopardize the ability to publish the results of the research in peer review journals; it would foster unscientific conclusions without peer review; an investigator cannot control the peer review process to ensure publication; it could negatively influence future trial recruitment and force a sponsor to disclose proprietary information. Several comments suggested that in multicenter studies, one institution may get a negative result, while another may get a positive result; thus, disclosure could be misleading. Comments suggested that updating the disclosure

could be burdensome and that the disclosure itself could be considered dissemination of off-label use information and advertising. Another comment questioned the need for such disclosure because the community would have no opportunity to modify the research; another commented that the disclosure would be so delayed and the community to which the disclosure would occur has such insufficient knowledge to understand the disclosure, that the disclosure would be meaningless.

Some comments requested that the agency define what and how disclosure is to be accomplished; what is "sufficient" and what would constitute the "scientific community." One comment questioned whether the information that would be disclosed to the community and researchers would differ.

The comments opposed to this disclosure requirement illustrate a need for the agency to clarify what is intended by this section. For a multicenter investigation, the agency anticipates that the sponsor and/or lead investigators will be responsible for analyzing the results of the overall investigation, including the demographic characteristics of the research population, and that these results will be published (or reported in the lay press) within a reasonable period of time following completion of the investigation. Publication in a scientific journal or reports of the results by lay press, that would be supplemented upon request by comprehensive summary data, will enable the research community, e.g., researchers not connected to the clinical investigation, to learn of the research's results. Following publication, the IRB will be responsible for determining appropriate mechanisms for providing this information, possibly supplemented by a lay description, to the community from which research subjects were drawn. The usual rules of marketing and promotion apply to the disclosure of this information. The agency notes that it is common for the results of research to be reported in the lay press and published in peer reviewed journals.

77. One comment noted that the comment in the preamble that there would be a need for fewer subjects if disclosure took place did not recognize the possible need for replication of the research—a sound scientific principle.

In the preamble to the proposed rule, the agency stated that: "[b]y broadly sharing the results of the research with the scientific community, there may be less need to replicate the research; therefore, fewer subjects may be needed

to obtain the same level of scientific knowledge and to advance emergency medicine." The agency recognizes that there is frequently a need to replicate research in order to verify its findings. The agency thinks, however, that broadly sharing both positive and negative results of research with the scientific community may reduce or eliminate unnecessary duplication of research that has been conducted and verified by others.

7. Section 50.24(a)(5)(iv)—Data Monitoring Committees

A number of comments on proposed § 50.24(a)(5)(iv), which has been renumbered § 50.24(a)(7)(iv) in this final rule, supported the requirement for the establishment of an independent data monitoring committee. These comments also requested clarification of the requirement and offered various suggestions. A discussion of these comments and the agency's response follows.

78. Editorial changes were suggested to this section to clarify the function of the data monitoring committee.

The regulation has been changed to clarify that the purpose of the data monitoring committee is to exercise oversight of the clinical investigation. In addition, on the agency's own initiative, the agency has changed "data and safety monitoring board" to "independent data monitoring committee" to conform to wording used in the international community.

79. Clarification was requested on the function, nature, authority, and responsibility of the committee. One comment requested citations to reference materials on data monitoring committees; another suggested that the regulation reference FDA's "Guideline for the Monitoring of Clinical Investigations" (53 FR 4723). One comment questioned whether the committee was simply advisory or whether it would have authority to halt a study. Other comments requested advice on the appropriate composition of the committee and another requested that FDA define its minimum size and expertise.

A number of comments requested clarification as to who is responsible for establishing and operating the data monitoring committee. One comment suggested that if it is the responsibility of the sponsor to establish the committee, then the term "independent" needs to be defined. Several comments noted that if the responsibility for establishing the committee changes, depending upon whether the study is multicenter with a commercial sponsor or a single center,

noncommercially sponsored study, the circumstances for this shift in responsibility must be clearly described. Another comment asked for clarification as to who is responsible for establishing "the preestablished stopping rules" and how these rules are defined. Several comments suggested that it should be the responsibility of the principal investigator and/or the sponsor of the research to convene the committee. Another comment suggested that if it is the responsibility of the sponsor to convene the committee for multicenter studies, it should be explicitly stated in the regulations.

A number of suggestions were given for how the committee should be composed and its functions. The agency also received suggestions for alternatives to the establishment of such a committee. Several comments suggested that the IRB be responsible for approving the composition of the committee based on the complexity, size, and risks associated with the study. Others suggested that the committee should be composed of specific types of individuals, including scientists, community members, IRB representatives without a conflict of interest, data management representatives, biostatisticians, and noninvestigator clinicians. Others suggested that a link be created between the committee and the IRB and that specific reporting requirements between the two entities be established so that the IRB can have the necessary information to terminate or modify the study.

The agency recognizes that there is no clear consensus within the scientific community regarding the optimal model for data monitoring committees. It is not the intention of the agency to settle the debates that are ongoing in the scientific community at this time. Rather, the agency recognizes that there is diversity in this area; the role, functions, and responsibilities of data monitoring committees are evolving, and it may be the case that there is no single model that is optimal in all circumstances. The data monitoring committee is established by the sponsor of the research, as an advisory body to the sponsor. An independent committee is constituted of individuals not otherwise connected with the particular clinical investigation. A variety of expertise is required for an effective data monitoring committee. Typically included are clinicians specializing in the relevant medical field(s), biostatisticians, and bioethicists. The data monitoring committee receives study data on an ongoing basis on a schedule generally defined in the investigational protocol;

based on its review of the data it may recommend to the sponsor that the clinical investigation be modified or stopped. In effect, it is responsible for making sure that continuing the investigation in its current format remains appropriate, on both safety and scientific grounds. A number of reasonable models for establishment and function of these committees are described and discussed in S. Ellenberg, N. Geller, R. Simon, S. Yusuf (editors), *Practical issues in data monitoring of clinical trials* (Proceeding of an International Workshop) *Statistics in Medicine*, vol. 12; 1993. If a sponsor accepts a data monitoring committee's recommendation to stop the investigation or to institute a major modification of the trial, the sponsor is required to notify FDA and all participating investigators and IRB's in a written IND or IDE safety report within 10 working days after the sponsor's initial receipt of the information. (See §§ 312.32, 312.56(d), and 812.150(b)(1)).

Protocols frequently contain statistical guidelines for permitting trials to stop prior to completing the protocol-specified accrual and followup, on the basis of definitive efficacy or safety differences between the treatments being compared.

80. Comments opposed to this requirement mainly cited concern that for single project/single institutional studies without a commercial sponsor, the cost and resources required for establishing such a body would be prohibitive and, therefore, important research would not be done. Another comment suggested that for noncommercially funded studies, the agency permit the investigator/sponsor to request a waiver of the requirement to FDA. If such a waiver were granted, timely data summaries could be submitted to FDA for review.

The agency disagrees with these comments. Trials of life-threatening conditions may discover favorable or adverse effects on survival during the trial. Requiring a data monitoring committee will help ensure that if it becomes clear that the benefits of the investigational intervention are established, or that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the investigation can be modified to minimize those risks or the clinical investigation can be halted. The data monitoring committee is established by the sponsor of the research, as an advisory body to the sponsor. It is the appropriate role of the sponsor, not FDA, to receive and evaluate a data monitoring committee's

recommendation. The agency thinks that a data monitoring committee is a very necessary protection for the human subjects participating in this research. The agency thinks that the cost of operating such committees does not need to be prohibitive and that the cost is justified by the protections provided by having such a committee.

81. Others commented that the requirement for a data monitoring committee is unnecessary given that these studies already will have oversight by FDA and the IRB, both of which are independent of the research, as well as by the sponsor and the clinical investigator.

The agency disagrees. The FDA, IRB, and research sponsor, unlike the data monitoring committee, do not receive outcome data from the clinical investigation on an ongoing basis. Thus, oversight by these entities does not substitute for the requirement for a data monitoring committee.

82. Another comment pointed out that there was no need for such a committee for nondrug and nondevice studies if these involved no more than minimal risk.

This regulation is applicable only to clinical investigations involving products regulated by FDA.

83. One other comment suggested that this requirement would be unduly burdensome unless the sponsor paid for the cost of establishing and operating the committee (including paying for the salaries of members on the committee).

As discussed previously, FDA does not prescribe what entity pays for particular aspects of clinical research and review. However, if, as previously described, the data monitoring committee is established by the sponsor of the research as an advisory body to the sponsor, the agency believes that it is likely that the sponsor will pay the cost of establishing and operating the committee.

84. Another comment suggested that the make-up of the data monitoring committee should not be left to the sponsor or clinical investigator to decide and that "independent" should be defined as "separate" from the research team and sponsor. Another comment noted that financial interest is only one aspect of what constitutes a conflict of interest and that the preamble to the final rule should clarify both terms when describing what constitutes an "independent" committee.

The agency believes that the 1993 *Statistics in Medicine* publication of the proceedings of an international workshop (previously referenced) will assist sponsors in establishing

appropriate data monitoring committees. As previously discussed, a variety of expertise is required for an effective data monitoring committee; the agency believes that it would be inappropriate for it to dictate the specific make-up of each such committee. In the preamble to the proposed rule, the agency defined "independent" to mean that the committee would be composed solely of individuals who have no financial interest in the outcome of the clinical investigation, and who have not been involved in the design or conduct of the investigation. The agency does not think that further clarification of "independent" is needed, but other factors can certainly be taken into consideration in individual cases.

85. One comment stated that the data monitoring committee should be charged with monitoring the makeup of the study population to ensure that it does not disproportionately consist of disadvantaged groups.

There is nothing to prevent a data monitoring committee from performing this type of monitoring. It is the responsibility of the sponsor to determine the scope of the data monitoring committee's responsibilities.

86. Some comments suggested alternatives to requiring the creation of a data monitoring committee, including requiring more frequent continuing review by the IRB or permitting a sponsor's monitor to perform the function. For noncommercially funded studies, it was suggested that the agency permit the IRB, with scientific and statistical consultants if needed, to perform the function.

An IRB, as well as a sponsor's monitor, may not have access to study data on an ongoing basis and may not have the variety of expertise required for an effective data monitoring committee. If an IRB, a subcommittee of the IRB, or some other preexisting institutional committee were to serve as a data monitoring committee, it would need to be constituted as a data monitoring committee when it functions in that capacity. The agency thinks that the duties and scope of activities of an IRB and a data monitoring committee are quite different and that it is important for separate entities to be established. The agency would not object, however, to an already established committee, such as an IRB, serving as a data monitoring committee as long as that committee was constituted to perform the duties of a data monitoring committee and operated as such separately and distinctly from its IRB activities.

87. As described previously, the agency has added a new section, § 50.24(a)(7)(v), to provide an additional protection to research subjects. This new section clarifies that if obtaining informed consent is not feasible and if a legally authorized representative is not available, the investigator will attempt to contact a family member of the subject to determine whether the family member objects to the subject's participation in the clinical investigation.

8. Section 50.24(a)(6)

88. Several comments were received on § 50.24(a)(6). One comment questioned whether the statement "obtaining such consent may be feasible for some subjects" referred to a circumstance in which obtaining consent may become feasible.

This comment did not take into account § 50.24(b). Section 50.24(b) concerns providing information to the subject, representative, or family member at the earliest feasible opportunity. Section 50.24(a)(6) is included to cover those instances where it may be feasible to obtain informed consent from the individual subject or subject's representative or contact a family member prior to entry into the clinical investigation.

89. Two comments suggested specific wording changes to acknowledge the IRB's responsibility to review informed consent procedures. One suggested that this section be reworded to state:

The IRB has reviewed and approved informed consent procedures and an informed consent document for subjects or their legal representatives in situations where use of such procedures and documents is feasible.

The agency has incorporated wording similar to that suggested into the regulation. It is appropriate to recognize the informed consent process, and not just the document, as requiring IRB review and approval. In addition, in order to help ensure that the family member has sufficient information to make a decision about a subject's participation in a trial, the agency has added a sentence to the end of § 50.24(a)(6) that states "[t]he IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section." The agency anticipates that these procedures and information will likely parallel those approved by the IRB for use in obtaining informed consent from subjects or their legally authorized representatives.

90. A second comment suggested that this section be replaced with the following:

The IRB has reviewed and approved: (i) the informed consent document and procedures to ask for informed consent by subjects or legally authorized representatives when obtaining such consent may be feasible for some subjects, (ii) the information provided and process to ask for a decision by subject or legally authorized representative to continue or discontinue participation after the research has begun, (iii) the information provided and procedures for consultation with representatives of the community, (iv) the information provided and procedures for public disclosure before the research, and (v) the information provided and procedures for public disclosure of the results of the research. All documents and procedures should also be submitted to the FDA for review.

This modification would require both the IRB and FDA to review and approve all documents or procedures that give information to the public, subjects, or representatives. The comment suggesting this modification notes that this is currently required for all nonemergency IND and IDE research.

The language suggested in this comment appears to duplicate requirements already contained in the regulation, that is: the requirement for review of informed consent documents is already contained in § 50.24(a)(6); the requirement for review of information concerning the subject's ability to discontinue participation in the research is contained in § 50.24(b); and the requirements for review of information used during consultation with or disclosure to the community are contained in § 50.24(a)(7)(i) to (a)(7)(iii). FDA has confidence in the IRB review process and does not think that it is necessary for all of these documents and procedures to be submitted to FDA for its review. The agency notes that conforming amendments to this regulation require that a copy of the information publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) be submitted to the IND or IDE file and to Dockets Management Branch. The agency further notes that the statement that FDA currently requires all of these documents and procedures to be submitted for its review for all nonemergency IND and IDE research is incorrect. Rather, it is the IRB that traditionally reviews information that is to be provided to the research subject; the requirements for consultation with and disclosure to the community have not been previously required.

9. Section 50.24(b)

91. A number of comments were received on § 50.24(b) that suggested

clarifying or tightening the requirement for informing subjects or their legal representatives. One comment recommended that the agency change the wording from "at the earliest possible opportunity" to the "earliest feasible opportunity." Another comment suggested that the timeframe for notification was too open-ended and that there should be a specific time limit.

The agency agrees with the wording change and has incorporated it into the regulations. The term "feasible" incorporates the idea of "practicability" and recognizes that in some instances it may not be feasible to provide information to the subject (e.g., if the individual does not survive or is mentally incompetent), and to the subject's legal representative or family member (if the identity of the subject is never determined). The agency also thinks that the phrase "at the earliest feasible opportunity" establishes a reasonable time limit.

92. Another comment suggested deleting the initial phrase "when possible and," noting that if the subject does not survive and no representative is found, then there will be no "opportunity" for a debriefing—thus, the initial phrase is not needed.

The agency agrees with this comment and for the reasons addressed in the previous response, has deleted this initial phrase from the regulation.

93. One comment suggested that the regulation require that if a representative is told and the subject's condition improves, the subject must also be informed as soon as possible. Two comments stated that if the subject dies, the subject's legal representative or family member must be provided with this information.

The agency agrees with these comments and has modified § 50.24(b) to state:

If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

94. A few comments suggested that § 50.24(b) be revised to require documentation that the subject, authorized representative, or family member, were informed of the research. Another comment suggested that the agency require a signed consent

document for continued participation in the research.

The agency thinks that it may not always be possible to develop a meaningful informed consent document for continued participation in the research, because the relevant information may vary significantly depending upon when it becomes feasible to provide the information to the subject or legally authorized representative. The agency is, therefore, not requiring that such a form be developed. The agency notes, however, that § 50.24(a)(6) places the responsibility on the IRB to review and approve "informed consent procedures and an informed consent document" for use with subjects or their legal representatives, and procedures and information to be used in consultations with family members, in situations where use of such procedure is feasible. Thus, a consent form will have been reviewed and approved for use in the clinical investigation. The agency has modified the wording in § 50.24(b) to specify that the "information contained in the informed consent document" is to be provided to the subject, legal representative, or family member. This will help to ensure that adequate information is provided to the subject, legal representative, or family member upon which a judgment can be made as to whether to continue or discontinue the subject's participation in the investigation.

It is up to the IRB to determine whether it is possible or desirable, given the nature of the clinical investigation, to have an actual document that could be signed for continued participation in the investigation. The agency notes that such a document, that would be signed after entry into an investigation, would not constitute consent for what had already occurred; it could, however, serve to document that the subject consented to continued participation in the investigation. The agency notes that §§ 312.60 and 812.140 require the clinical investigator to document data pertinent to each individual in the investigation. This documentation should include information that the subject, legally authorized representative, or family member was informed of the subject's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document.

95. One comment on the subject's ability to discontinue participation in the research suggested that § 50.24(b) be reworded to state:

The subject or legally authorized representative should be presented with three options: continue fully, continue the intervention (if it is still taking place) but do not include the subject's data in the research database or results, or discontinue both the intervention and the use of the subject's data. The researcher will track the percentage of subjects or representatives choosing each option.

FDA regulations (see, for example, § 312.62 and § 812.140(a)(3)) require investigators to prepare and maintain adequate case histories recording all observations and other data pertinent to the investigation on each individual treated with the drug or exposed to the device. The agency needs all such data in order to be able to determine the safety and effectiveness of the drug or device. The fact of having been in an investigation cannot be taken back. Also, if a subject were able to control the use (inclusion and exclusion) of his or her data, and particularly if the clinical investigation were not blinded, the bias potential would be immense. Thus, the agency rejects this comment because it could prevent FDA from learning of an important effect of the product and significantly bias the results of the investigation.

96. One comment noted that in cases where withdrawal from a study would be life-threatening, FDA might consider additional guidance on counseling of subjects who have regained competence regarding their remaining in the study. Another comment noted that in some cases, a subject cannot be withdrawn from the study, particularly in the case of an implanted device, without some degree of medical harm—that is, the possibility of additional risk for the subject due to its removal. In this case there is a “penalty” for withdrawal from the research.

In all clinical investigations, when appropriate, it is the responsibility of an investigator to advise the subject of the consequences of a subject's decision to withdraw from the investigation and explain procedures for orderly termination of participation by the subject. (See § 50.25(b)(4)). If withdrawal from an investigation would or could be life-threatening, this consequence would need to be conveyed to the subject. The agency acknowledges that for certain interventions, such as implantation of an investigational device, there may be a serious consequence following a subject's decision to discontinue participation in the research. Similarly, for an investigational drug that cannot be halted immediately without medical consequences, the subject will need to be advised of the consequences of a

decision to withdraw and procedures for withdrawal that would minimize risks to the subject.

10. Section 50.24(d)

A number of comments expressed concern about § 50.24(d) requiring a separate IND or IDE for studies conducted under § 50.24 if an IND or IDE already exists. Others expressed concern about requiring an IND or an IDE for products that have received FDA approval for other uses.

97. One comment suggested a modification to the wording of § 50.24(d) to state that: “[s]uch IND or IDE should only include enough detail to satisfy the administrative oversight responsibilities of appropriate FDA officials.”

The agency disagrees with this suggestion. The information that is required to be in an IND or IDE is the information that is needed by the agency to conduct an adequate review of the application. As described in more detail below, if an IND or IDE exists, the separate application does not need to duplicate, and the sponsor does not need to resubmit, information that is contained in the existing IND or IDE; the separate application will need to reference the existing IND or IDE, contain a protocol for the clinical investigation that includes a description of how the investigation proposes to meet the conditions of this regulation, and contain only the study-specific information required by §§ 312.23, 812.20, and 812.25, as appropriate.

98. A number of comments suggested alternative approaches to the requirement contained in § 50.24(d) for products that have received marketing approval or for which there already exists an IND or IDE, noting that for these studies this requirement would be unduly burdensome, would create the need for unnecessary paperwork, and could effectively prohibit much needed research. One comment suggested that the agency limit the scope of this requirement or consider an alternative for single-center studies under which an IRB can waive consent if the investigator has informed the appropriate branch of FDA of the proposed study at least 30 days before submission to the IRB to allow FDA time to submit its views on the study for consideration by the IRB. This comment argued that such a requirement would provide sufficient opportunity for FDA involvement, while at the same time permit a focused FDA review, consuming fewer resources than would the review of an IND or IDE for each study. Other comments suggested that the agency has ample authority under

existing IND and IDE regulations to require strict adherence to the 30-day review period and that the agency should simply require that emergency research protocols be clearly identified as such, submitted to the agency under an existing IND or IDE, and be unable to commence until 30 days after submission. These comments argued that this would meet the objective of the regulation without adding additional administrative burdens to the sponsor or investigator.

These comments may not appreciate why the agency is requiring the submission of an IND or IDE for each clinical investigation and the information that must be contained in such an IND or IDE. The submission of a separate IND or IDE will ensure that FDA reviews the application before the study may proceed. FDA review of the application will enable the agency to assess whether the available treatments for the condition are unproven or unsatisfactory, whether the intervention is reasonable, whether the study design will provide the information sought, and whether other conditions of the regulations are met. The amount of information needed in the application will differ depending upon the particular intervention. If an IND or IDE exists, the separate application does not need to duplicate, and the sponsor does not need to resubmit, information that is contained in the existing IND or IDE; the separate application will need to reference the existing IND or IDE, contain a protocol for the clinical investigation that includes a description of how the investigation proposes to meet the conditions of this regulation, and contain only the study-specific information required by §§ 312.23, 812.20, and 812.25, as appropriate.

If the investigation involves a product that has received marketing approval and the use is within the product's approved labeling, and without dosage or schedule change if for a drug product, the protocol may simply need to be accompanied by the product's approved labeling and a description of how the investigation proposes to meet the conditions of this regulation; no toxicology or manufacturing controls or chemistry information may need to be submitted. By submitting this information to the agency for review, the dual review by both FDA and an IRB will provide additional protections to the subjects of this research. The agency does not think that this requirement is unduly burdensome, creates unnecessary paperwork, or would prohibit needed research.

If the clinical investigation involves a product that has received marketing

approval, but involves a route of administration or dosage level or use in a subject population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product, or if the investigation involves an investigational product for which an IND or IDE does not exist, then the IND or IDE would need to include information to support the altered conditions of use, including toxicology, chemistry, and clinical information, as appropriate.

99. Another comment suggested that the agency should: (1) Include a mandatory internal "ethics consult" of the protocol and informed consent (this would necessitate requiring the submission of proposed informed consent documents with the IND/IDE application); (2) ensure that data on these submissions are captured in a readily retrievable form for future analysis and reporting so that information on the types and numbers of such submissions will be available; (3) be able to provide names and contact information for IRB's reviewing these protocols to ensure communication among these IRB's; and (4) respond actively in writing to any submission under these regulations either placing the study on "clinical hold" or indicating that the agency's review has been completed. This would ensure that the agency has completed its review before the study is permitted to proceed.

The agency's response to each of these suggestions follows: (1) The agency believes that it would be inappropriate to mandate an internal agency "ethics" consultation on each protocol proposing to invoke this exception from informed consent. It is within the province of the IRB to determine the ethical acceptability of a proposed clinical investigation. The agency does intend, however, to periodically review actions on these protocols to help ensure that the rule is implemented consistently and appropriately throughout the agency. The agency notes that under the IDE regulations the agency requires the submission of the proposed informed consent documents with the IDE application. (2) FDA thinks that it can best monitor the implementation of this rule by requiring the submission of a separate IND or IDE for these clinical investigations. By requiring the submission of a separate IND or IDE for these investigations, FDA expects to be able to provide information on their type and number. (3) The agency believes that it would be more appropriate for the sponsor of the research to facilitate communication among reviewing IRB's, instead of FDA

performing this function. (4) FDA agrees that it should provide a written response to the sponsor following the agency's review of these protocols. FDA currently sends written responses following review of IDE's and treatment IND's and believes that sending letters here will serve as an additional protection for subjects. The response will serve to document that FDA has reviewed the clinical investigation and agreed that it may proceed, and the letters will result in the ability of sponsors to begin these investigations as expeditiously as possible. The agency has added language to §§ 312.20(c) and 812.20(a)(4)(i) to clarify that a clinical investigation involving an exception from informed consent under § 50.24 is not permitted to proceed without the prior written authorization from FDA. FDA will provide such notification 30 days after FDA receives the application, or earlier.

100. Section 50.24(d) raised a number of questions and caused confusion concerning its applicability to: Studies designed to compare the efficacy of two already marketed agents; the study of systems, processes, and procedures that are not designed to assess the efficacy of a test agent, but rather to determine the best process or technique for its use; a study comparing the effect of a standard of care with the use of no agent at all; and FDA exercising jurisdiction over studies that do not involve evaluating the safety or efficacy of a product subject to FDA regulation. One comment recommended that the regulations be expanded to apply to not only new devices or drugs, but also to new uses for existing devices and drugs, as well as to new therapeutic techniques and that researchers be permitted to seek FDA approval for research on drugs or devices already in use through alternate forms and/or procedures developed by FDA for this purpose.

This comment incorrectly interpreted the wording in § 50.24(d) to apply only to unapproved new devices or unapproved new drugs. As discussed earlier, § 50.24(d) also applies to clinical investigations involving already marketed products that are regulated by FDA. This regulation does not apply to research that is outside of FDA's regulatory jurisdiction—that is, studies involving no product subject to FDA regulation.

101. A number of examples were provided of studies that purportedly would have been prevented if an IND or IDE had been required: (1) High versus low dose epinephrine; (2) interposed abdominal counterpulsation CPR; (3) saline infusion during trauma; (4) effect of high pressure ventilation during CPR;

(5) studies on sodium bicarbonate during CPR; (6) studies on MAST trousers during CPR; and (7) comparison of various intravenous crystalloid solutions in shock-trauma. The application of this requirement to these types of studies was described, by at least one comment, as the "fatal flaw" in the regulation. Other comments suggested that the broad scope of this requirement would be wasteful of sponsor resources in terms of filing the IND and IND annual reports, wasteful of FDA resources in terms of reviewing such studies, cause unnecessary paperwork, and would suppress necessary studies.

As discussed previously, the agency believes that it is necessary to require an IND or IDE for these types of clinical investigations and it does not believe that this requirement is unduly burdensome or that it will prevent needed research. The information required in a sponsor's annual report would not increase because of the requirement for a separate IND or IDE. The sponsor would simply need to prepare a separate cover letter and excerpt the information from the other IND's or IDE's annual report, and file it in the separate IND or IDE.

102. Several comments suggested that the IND/IDE regulations could be revised to allow for a 30-day review period for those studies that qualify for this exemption; that sponsors would voluntarily agree to wait 30 days for agency review of such studies; or that the agency could place "on hold" for 30 days such studies in order to allow for agency review.

FDA thinks that the most efficient way for the agency to ensure that these clinical investigations are reviewed by the agency before they commence is to require the submission of a separate IND or IDE for that investigation. FDA is concerned that to allow these investigations to be submitted as amendments to existing IND's or IDE's could be confusing to sponsors and might lead to these investigations beginning before FDA review. This is because the agency's current regulations do not require a 30-day wait for amendments; they can begin immediately following submission to the agency and receipt of IRB approval. The agency thinks that this is a simple and nonburdensome mechanism that achieves an important protection for subjects in this research in which subjects may be enrolled without informed consent.

11. Section 50.24(e)

103. Most of the comments on § 50.24(e) objected to FDA modifying

the traditional reporting/information flow from IRB to clinical investigator to sponsor and the reverse. These comments requested that the agency retain this flow of communication in the rule.

The agency disagrees with these comments. Although FDA recognizes that the sponsor's interaction with the IRB should primarily occur through the investigator who conducts the clinical investigation, FDA has never prohibited direct communication between the sponsor and the IRB when doing so would result in a more efficient flow of information. For clinical investigations involving medical devices, FDA requires direct communication between the sponsors and the IRB's in a number of instances. (See, for example, multiple paragraphs in § 812.150(b).) The agency thinks that it is appropriate for the IRB to communicate directly with the sponsor and for the sponsor to communicate directly with the IRB when this improves efficiency and/or safety, as it does in this regulation. The agency has amended this section and its related conforming amendments to specify that the IRB shall document its findings and provide them promptly in writing to the investigator and the sponsor of the clinical investigation when an IRB determines that it cannot approve the investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns. The agency thinks that this is the most efficient mechanism to ensure that both the investigator and sponsor are advised of the IRB's findings in a timely manner.

104. In a related comment, clarification was requested for studies in which there is no commercial sponsor and whether it is then the responsibility of the institution or the individual investigator to carry out the requirements specified in this section (as well as in the conforming amendments of §§ 56.109(g), 312.30, and 312.54).

Whether or not there is a commercial sponsor, each clinical investigation has a sponsor and it remains the sponsor's responsibility to carry out the requirements assigned to the sponsor in this section. (I.e., if the investigation is investigator-sponsored, the investigator is the sponsor of the research and, therefore, the investigator assumes all the responsibilities of the "sponsor.")

105. Another comment suggested that when an investigator is proposing a previously IRB-rejected protocol, the investigator is ethically obligated to disclose the rationale of the earlier rejecting IRB.

The agency agrees with this comment, but it believes that no change is needed in the regulations. The requirements in § 50.24(e) will compel a sponsor to disclose to IRB's that have reviewed or are asked to review a clinical investigation the findings of an IRB that could not approve the investigation because the investigation does not meet the criteria in this exception provided under paragraph (a) of § 50.24 or because of other relevant ethical concerns.

106. Another comment suggested that in order to avoid delay or failure to convey information about previously disapproved protocols, the IRB should submit information directly to FDA.

The agency disagrees with this comment. The conforming amendments (§ 312.54(b) and § 812.47(b)) require a sponsor to monitor these studies to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in § 50.24(a) or because of other relevant ethical concerns, and to promptly provide this information in writing to FDA. The sponsor is, therefore, obligated to submit this information promptly to the agency.

107. Another comment suggested that sharing IRB research rejection information compromises the autonomy of the IRB and that it will make impartial decision making more difficult.

The agency disagrees and believes that human subject protections will be enhanced by sharing of this information.

108. A number of comments and questions addressed the phrase "substantially equivalent clinical trials." Several comments noted that a given sponsor may not be aware of a substantially equivalent clinical trial proposed by another sponsor; thus, FDA and/or OPRR should be responsible for ensuring that communication about such trials takes place. One suggestion was for FDA to establish an on-line registry at FDA of studies that have applied for waiver of consent; this registry could be searched by IRB's and investigators to determine which other IRB's have reviewed the same or substantially equivalent trials.

The agency intended this requirement to refer to clinical trials with the same sponsor. The regulation has been modified to clarify this issue.

109. One comment suggested that the extent of this reporting (of "disapproval" information) should be defined in the preamble, with the minimum content of such a report contained in the regulation.

Existing § 56.109(d), redesignated as § 56.109(e) requires an IRB to "notify

investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity." It states that "[i]f the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision.* * *" The new sentences to § 56.109(e) requires the IRB to notify the investigator and sponsor in writing when an IRB determines that it cannot approve the research because it does not meet the requirements of § 50.24(a) or because of other ethical concerns. FDA has revised the wording of § 56.109(e) to make it explicit that this written notification must include a statement of the reasons for the IRB's determination. The correspondence from the IRB should contain sufficient information for a receiving IRB to understand the concerns of the initial IRB.

110. One comment noted that if it is the agency's concern that a sponsor may minimally modify the rejected proposal (i.e., a substantially equivalent trial) and submit it to another IRB, that should be clarified and prohibited. Another questioned whether "equivalent" referred to medical conditions, treatments compared, subject populations, or something else. Another comment questioned whether "substantially equivalent" only applies to other trials with the same drug/device; if the sponsor subsequently requests an exemption for a similar trial with another drug in the same class must the sponsor disclose the IRB findings about the first drug.

By "substantially equivalent" the agency means other clinical investigations that propose to invoke this exception from informed consent and that involve basically the same medical conditions and investigational treatments. As noted previously, the agency intends this requirement to refer to clinical investigations conducted by the same sponsor.

111. Another comment questioned who is expected to make the determination that a study is "substantially equivalent." This comment described a potential situation whereby an IRB rejected a protocol as written and the sponsor then modified the protocol according to the IRB's recommendations. This comment, as well as others, questioned whether, in a multicenter study, the other centers that approved and initiated the initial protocol would have to review this trial again.

It is the sponsor's responsibility to determine that a study is "substantially

equivalent." If, in the scenario described, a protocol invoking this exception is modified by the sponsor in order to respond to IRB concerns that it does not meet the criteria in § 50.24(a) of the exception or because of other relevant ethical concerns, and it is a multicenter study, then the IRB's written findings are to be disclosed to other centers that either are, or may be, participating in the study. If there is a change in a protocol in a multicenter trial, there is re-review of the protocol by all the IRB's of the institutions participating in the multicenter trial. If the change is minor, it may be eligible for expedited review under § 56.110, which permits the IRB to use an expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. If the change is significant, it would need to be reviewed by the full committee. It is the sponsor's responsibility to determine if it has a substantially similar protocol necessitating information dissemination.

112. One comment noted that the current wording of § 50.24(e) appeared to require disclosure of IRB disapprovals only to future IRB's and investigators. This comment suggested that the regulation should specify that investigators already participating and IRB's that have already approved the study be notified of an IRB disapproval.

The agency agrees with this comment and has modified § 50.24(e) accordingly. The agency thinks that this information is relevant to IRB's that have reviewed and approved the study and that will be responsible for conducting continuing review of the research as well as to IRB's that will be asked to review the study. Although this information may not change an IRB's final determination on the approvability of a particular protocol, it will allow access to, and the ability to consider, information that negatively influenced another IRB.

113. Several comments questioned the timing of IRB review and submission of the IND. One comment suggested that IRB review precede the submission of the IND to prevent agency review of studies that would eventually be found to be unacceptable to the reviewing IRB's. This comment suggested that the regulations be modified to indicate that if an IRB refuses to approve the study, the sponsor could request a pre-IND meeting with FDA to discuss the reasons for the disapproval. Another comment suggested the opposite, noting that many IRB's will not consider a protocol under an IND or IDE until after FDA approval because FDA review includes aspects that are not within the

scope of IRB review. Thus, FDA should agree to review and approve IND's and IDE's that contain a firm and binding sponsor commitment to local IRB review. This comment noted that implementation of the § 50.24(a) provisions will be policed by OPRR and, thus, both FDA and the public can be ensured that the sponsor's advance commitment will be met. This comment suggested the following language:

§ 312.40(b)(3) For a separate IND submitted under § 312.20(c), if a sponsor provides a commitment to local IRB establishment and approval of procedures for compliance with § 50.24(a).

§ 812.30(a)(3) For a separate IDE submitted under § 812.20(a)(4), if a sponsor provides a commitment to local IRB establishment and approval of procedures for compliance with § 50.24(a).

§ 50.24(c) [Add the following sentences] The IRB must document the additional protections provided under subsection (a)(5) in writing to the sponsor of the research. The sponsor of the research must share this information with FDA.

The agency does not agree that it should mandate the timing of IRB and FDA review. As evidenced by the comments, sponsors currently differ in whether they request FDA or IRB review first. FDA does not believe it should reduce the sponsor's flexibility to determine the sequence of IRB and FDA review. The agency notes that FDA may find a clinical investigation unacceptable or require modifications in an investigation which, if it had been reviewed by an IRB, would require re-review by the IRB.

The comment concerning an IRB refusal to approve a study and the need for a pre-IND meeting does not explain the reason such a meeting should occur. As described in 312.47(a): "[m]eetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit." Thus, while there is nothing to prevent a sponsor from requesting a meeting with FDA, it is not clear that a sponsor would want to meet with the agency to discuss why an IRB did not approve its investigation.

In response to the comment that FDA should agree to review and approve IND's and IDE's that contain a firm and binding sponsor commitment to obtain local IRB review, FDA agrees. FDA will accept a sponsor's commitment in an IND or IDE application to obtain IRB review in this situation as it does in others. The agency understands that IRB

review may follow submission and review of the investigation by FDA. Thus, where an IRB has not yet reviewed and approved the protocol that the agency has reviewed and allowed to proceed, an IRB's review and approval, as well as community consultation and disclosure, are then required prior to subjects entering the investigation.

The agency notes that OPRR does not enforce the provisions in § 50.24(a) for clinical investigations that are regulated by FDA. Instead, FDA oversees the quality and integrity of the research that is conducted under the agency's jurisdiction through its Bioresearch Monitoring Program. FDA's Bioresearch Monitoring Program includes inspections of clinical investigators, sponsors, and IRB's to evaluate whether each entity's obligations are met.

Finally, the agency does not believe there is a need to adopt the additional language suggested regarding IRB review because the language is redundant with existing regulations, i.e., the regulations already require sponsors to obtain the investigator's commitment to obtain IRB review (see, for example, 312.53(c)(1)(vii)); IRB's are required to "find and document" each item under (a), including (a)(6)) (see § 50.24(a)); and IRB's are required to provide information that has been publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) to the sponsor and the sponsor is required to provide this information to FDA (see, for example, § 56.109(g), § 312.54(a), § 601.51(d), and § 812.38(b)(2)). In addition, as previously described, FDA expects the protocol for the investigation to include a description of how the investigation proposes to meet the conditions of this regulation.

114. A number of comments questioned the value of § 50.24(e) and suggested that it be deleted. The reasons given in these comments included: its impracticality, its irrelevance to local decision making, the inappropriate line of communication (previously discussed), and the precedent that it establishes for requiring public disclosure of IRB decision-making (potentially leading to extra liability from disclosure for the IRB). Comments also questioned whether the requirement would apply to unsponsored research (discussed above), noted that if FDA needs this information it can request it from the IRB, and asserted that it is inappropriate for the IRB to apparently review a study and give feedback to FDA when IRB's depend on FDA to conduct an adequate preliminary review of such studies. Comments also noted the paperwork

burden on IRB's (which may need to write a very different type of document than the one that it would typically write in rejecting a study), and that this requirement could undermine the authority of the IRB if it were obliged to report each rejection to FDA. One other comment questioned the value of this requirement noting that one IRB's decision to reject a study would have no impact on the substantive, factual medical and other information available to all IRB's. This comment noted that the relevance of this evaluation for an IRB that has already approved a study would be even more untenable and burdensome and could potentially be disruptive to the sponsor and ongoing studies. Another comment noted that this requirement is ambiguous and questioned whether the sponsor would need to provide the report exactly as provided by the IRB or whether the sponsor could summarize the IRB's findings. This comment also questioned how FDA would use this information.

The agency disagrees with these comments. The agency does not think that this will create an additional recordkeeping burden on IRB's because these findings are already required to be documented by the IRB under § 56.109(e) and § 56.115(a)(2). As noted earlier, the agency has modified this section to require the IRB to provide these findings to the clinical investigator and to the sponsor of the research. The agency has a great deal of respect for the IRB system and for decision-making that occurs by IRB's. Given the nature of this research, the agency thinks that it is important for entities with responsibility for allowing these investigations to proceed to consider IRB concerns related to these investigations. The agency will expect the sponsor to forward the report exactly as it was provided by the IRB; however, the sponsor may choose to provide additional relevant information to the agency along with the IRB's findings. Similarly, if an IRB chooses to prepare more extensive documentation of its findings than that which is required by § 56.109(e), § 56.115(a)(2), and § 56.115(a)(4), there is nothing in this regulation that would prevent the IRB from so doing.

115. One comment noted that an IRB may reject a study based on the ethical criticism of a single member. This comment argued that if an IRB raised a relevant ethical issue, the sponsor, which is the entity with the greatest legal liability, should evaluate the issue and if the concern is found to be valid, it should be up to the sponsor to decide to communicate the issue to other IRB's. This comment suggested that abridging

the sponsor's responsibility will lead to less independent thinking by IRB's, slower progress in expanding clinical trials, and a "mass" of less than well-considered ethical comments being presented to FDA for its consideration.

The agency intends to monitor and evaluate the implementation of this regulation on an ongoing basis. While the agency doubts that such effects will be caused by this requirement, the agency will evaluate the impact of this requirement on IRB's and the conduct of clinical investigations. The agency notes that if an IRB "rejected" an investigation on the basis of an argument put forth by a single IRB member, it would appear likely that member's arguments were persuasive to the whole IRB.

116. The agency received a number of comments that suggested editorial or technical changes to clarify the language contained in the regulations.

The agency has incorporated editorial and technical changes where the agency thinks that they add clarification to the language in the regulation. In certain cases, the agency disagreed that the editorial or technical changes would clarify the language in the regulation.

C. Conforming Amendments

A variety of comments were received on the conforming amendments. Some of these have been previously discussed. Others, that relate solely to the conforming amendments, are discussed below.

117. One comment objected to § 56.109(c)(1) which allows an IRB to waive the requirement that the subject sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. This comment noted that one cannot ensure that informed consent is obtained, if a written consent form is not signed.

The language contained in § 56.109(c)(1) has been in effect since 1981 and applies to research that involves no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. This section does not apply to research conducted under the provisions of this rule.

118. One comment suggested that § 56.109(c)(2) be modified to include the suggestion that the IRB should seek additional input, as necessary, from sponsors or other experts to aid them in their decision making.

The IRB currently is free to consult with anyone that it wants; no change in the regulation is needed.

119. One comment on § 56.109(d) suggested that the discretion suggested by the use of the term "may" was inappropriate and that this term should be changed to "must" in order to require the investigator to provide subjects with a written statement. Another comment questioned whether the proposed § 56.109(d) replaced the current (d) or extended it.

Proposed § 56.109(d) was taken from the existing IRB regulation; it was the last sentence in § 56.109(c). Section 56.109(d) became proposed § 56.109(e) with an additional sentence added at the end. In writing this conforming amendment, the agency intended new § 56.109(d) to apply only to § 56.109(c)(1)—that is, to studies that involve no more than minimal risk and involve no procedures for which written consent is normally required outside the research context. The agency has modified § 56.109(d) to make this clear; on its own initiative, the agency has also corrected a typographical error in this paragraph. The agency notes that § 50.24(b) describes the requirements for emergency research.

120. One comment suggested that § 56.109(e) does not match the intent of § 50.24(e), in that not only the notice of disapproval, but also the reason and/or concern needs to be provided. This comment suggested that § 56.109(e) be modified to include the following sentence: "The written notification shall include a statement of the reasons for the disapproval."

The agency agrees with this comment and had intended that the reasoning behind the IRB's determination be provided. The agency notes that it is not only IRB disapprovals, but also an IRB's determination that it cannot approve an investigation, that triggers this requirement.

121. Another comment suggested that elsewhere in the regulations, there is allowance given for discussion between an investigator whose study has been disapproved and the reviewing IRB. This comment suggested that similar wording, or clarification, should allow for sponsor and IRB negotiation.

The agency disagrees with this comment. The purpose of this requirement is to enhance, not limit, communication of information between IRB's, investigators, sponsors, and FDA. § 56.109(d), renumbered as § 56.109(e), continues to state that "[i]f the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing." There is nothing in this regulation that prevents this

opportunity for discussion from occurring. It is up to the IRB, however, to determine when a final determination has been made on a study.

122. One comment questioned whether § 56.109(e) should be paragraph (f) (a new paragraph), referring only to documentation of refusals to approve.

Old 56.109(d) which concerns decisions to approve, disapprove, or modify research, was renumbered in the proposal as new section 56.109(e). Thus, this paragraph does address documentation of disapprovals.

123. One comment recommended that the responsibility for determining when disclosure has occurred be assigned to the IRB's and that IRB's should be required to notify the sponsor so that the sponsor could notify FDA. This comment would affect §§ 56.109(g), 314.430(d), 812.38(b)(2) and 812.47(a).

The responsibility for determining when information has been publicly disclosed is a dual responsibility of the IRB and sponsor. Section 56.109(g) requires the IRB to provide a copy of information that has been publicly disclosed to the sponsor of the research; the sponsor is responsible for notifying FDA. Sections 312.54(a) and 812.47(a) require the sponsor to monitor the progress of all research invoking § 50.24 to determine when the public disclosures occur and to promptly submit copies of the information that has been publicly disclosed to the IND or IDE file and also to the Dockets Management Branch.

124. One comment recommended that proposed section 56.111(c) be deleted, noting that this section is a documentation statement, rather than an approval criterion. This comment notes that proposed § 50.24(a) contains similar language requiring such documentation and, therefore, no benefit is evident in the proposed modification to § 56.111.

The agency agrees that there is no need for proposed section 56.111(c). Under § 50.24(a), the IRB is responsible for finding and documenting that each of the safeguards are met; this is also covered broadly by § 56.111(a)(4).

125. Several comments suggested that § 312.54(a) be modified to state that the "sponsor shall document" rather than "determine" when public disclosure has occurred. These comments suggested that "determine" could be misconstrued to mean that the sponsor shall "decide" what constitutes adequate public disclosure, and that it is the responsibility of the IRB to make that determination.

The agency agrees that it is the responsibility of the IRB to determine what constitutes adequate disclosure to the community; however, it is the

responsibility of the sponsor to provide copies of the information disclosed to the agency. The language in § 312.54(a) has been modified to clarify that when the sponsor receives from the IRB information concerning the public disclosures required by § 50.24(a)(7)(ii) and (a)(7)(iii), the sponsor is required to submit the information that was disclosed to FDA.

126. One comment recommended that the reference to § 50.23 be removed from § 312.60 but provided no explanation.

FDA rejects this comment and believes that the reference to § 50.23 in § 312.60 is needed to identify the various provisions in the regulations permitting an exception to informed consent. Because § 50.23 provides different criteria for permitting an exception to the informed consent requirement, the agency is retaining reference to this section in § 312.60.

127. One comment questioned the meaning of the modification to § 314.430 and whether it means that Freedom of Information (FOI) requests for this information will not be processed, or that requests for information publicly disclosed under § 50.24(a)(7)(ii) and (iii) must be submitted to the Dockets Management Branch.

Requests for copies of this public disclosure information are to be submitted as Freedom of Information Act requests. FDA has amended § 312.130(d), 314.430(d)(2), 601.51(d)(2), 812.38(b)(4), and 814.9 to clarify that persons wishing to request the publicly disclosed information in the IND or IDE that was required to be filed with the Dockets Management Branch shall submit a request under the Freedom of Information Act. Alternatively, persons wishing to view this information may visit FDA's Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. A special docket, Docket Number 95S-0158, has been established for this purpose. To facilitate retrieval of information that may pertain to a single clinical investigation, FDA is specifying that information submitted to the docket must be identified by the IND or IDE number.

128. This comment also suggested that § 312.130 be modified by the addition of

312.130(d) For investigational new drug applications involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) [renumbered § 50.24(a)(7)(ii) and (a)(7)(iii)] to the IND file and to Dockets Management

Branch. Copies of this information will be available to the public from the Dockets Management Branch.

The agency agrees with this comment that it would be clearer if § 312.130(d) were modified. Consistent with the discussion above, the agency has amended § 312.130 to add a new paragraph (d) which contains similar language to that suggested in the comment.

129. On the agency's own initiative, FDA is amending the clinical hold regulation at § 312.42 to explicitly include a failure to comply with the requirements in § 50.24 as a reason for clinical hold. The agency believes this revision will remove any confusion that may exist regarding the authority to stop, where warranted, an investigation invoking this rule. The agency does not believe a change is needed to the device regulation at § 812.30 on disapproving or withdrawing approval of an IDE because that regulation currently expressly authorizes FDA to take such action for failure to comply with "any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA."

D. Preemptive Effect

In developing these rules, FDA considered whether there were existing State or local legal requirements governing informed consent that might limit or preclude participation in research in circumstances that otherwise could be authorized by IRB's acting in accord with these proposed rules. FDA recognizes that nationally uniform informed consent requirements governing this type of research could serve to lessen the current confusion created in the research community by differing Federal regulations. FDA also recognizes that the existing Federal Policy for the Protection of Human Subjects, which governs much of this type of research, currently provides that it does not affect any State or local laws or regulations that may otherwise be applicable and that provide additional protections for human subjects. Accordingly, FDA specifically invited comment on whether there are existing State or local legal requirements that might limit or preclude participation in research in circumstances that otherwise could be authorized by IRB's acting in accord with these proposed rules and whether any such requirements should be preempted by Federal requirements. As discussed previously, FDA received limited information on existing State or local legal requirements that might limit or preclude participation in research covered by this rule. The agency also

received a number of comments in favor of the status quo. The information submitted on existing State or local legal requirements was insufficient for the agency to justify changing the existing Federal policy for the protection of human subjects, which governs much of this type of research, and which currently provides that it does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. Thus, the agency does not intend to preempt existing State or local requirements that provide additional protections for human subjects.

IV. Effective Date

These regulations are effective November 1, 1996. IND's and IDE's that intend to invoke this rule may be submitted to the agency on or after the publication date of this rule and must include a description of how the clinical investigation proposes to meet the conditions of this regulation. These investigations cannot begin until the rule is effective, the agency has reviewed the investigation against the requirements contained in this final rule, a letter has issued to the sponsor advising the sponsor that the investigation may proceed, the investigation has been reviewed and approved by an IRB, and the community consultation and disclosure required by this rule have occurred.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Executive Orders

A. Executive Order 12606: The Family

Executive Order 12606 directs Federal agencies to determine whether policies and regulations may have a significant impact on family formation, maintenance, and general well-being. FDA has analyzed this rule in accordance with Executive Order 12606, and has determined that it has no potential negative impact on family formation, maintenance, and general well-being.

FDA has determined that this rule will not affect the stability of the family, and particularly, the marital commitment. It will not have any significant impact on family earnings. The rule would not erode the parental

authority and rights in the education, nurture, and supervision of children.

B. Executive Order 12612: Federalism

Executive Order 12612 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant effect on Federalism. Using the criteria and principles set forth in the order, FDA has considered the rule's impact on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government. FDA concludes that this rule is consistent with the principles set forth in Executive Order 12612.

Executive Order 12612 states that agencies formulating and implementing policies are to be guided by certain Federalism principles. Section 2 of Executive Order 12612 enumerates fundamental federalism principles. Section 3 states that, in addition to these fundamental principles, executive departments and agencies shall adhere, to the extent permitted by law, to certain listed criteria when formulating and implementing policies that have federalism implications. Section 4 lists special requirements for preemption.

Section 4 of Executive Order 12612 states that an executive department or agency foreseeing the possibility of a conflict between State law and federally protected interests within its area of regulatory responsibility is to consult with States in an effort to avoid such conflict. Section 4 of the Executive Order also states that an executive department or agency proposing to act through rulemaking to preempt State law is to provide all affected States notice and opportunity for appropriate participation in the proceedings. As required by the Executive Order, States have had, through this rule's notice of proposed rulemaking, an opportunity to raise the possibility of conflicts and to participate in the proceedings (section 4(d) and (e)). Consistent with Executive Order 12612, FDA requested information and comments from interested parties, including but not limited to State and local authorities, on these issues of federalism. FDA is not preempting State law through this rulemaking.

VII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is

necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The agency has determined that this rule is a "significant regulatory action" as defined in section 3(f)(4) of the Executive Order because it raises novel policy issues.

If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This rule is a deregulatory action insofar as it will permit research to proceed that could not proceed under existing regulations, and because relatively few research projects will need to meet the requirements of this rule. Therefore, under the Regulatory Flexibility Act 5 U.S.C. 605(b), the Commissioner certifies that the rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VIII. Paperwork Reduction Act of 1995

This rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Pub. L. 104-13, May 22, 1995), and that are already approved under Protection of Human Subjects—Recordkeeping Requirements for Institutional Review Boards, part 56 (21 CFR part 56) under OMB Control No. 0910-0130; Investigational New Drug Application under OMB Control No. 0910-0014; and Investigational Devices Exemption Reports and Records, part 812 (21 CFR 812) under OMB Control No. 0910-0078. Modifications to these approved information collection requirements are underway or will be made at the time that each information collection is renewed. The agency believes that this is appropriate because this rule has only a minor impact on these existing information collection packages.

One comment was received on the agency's estimate of paperwork burden. That comment noted that the estimate of 20 sponsored investigational drug and 10 sponsored device studies that will require waiver of consent may be correct for multicenter studies sponsored by manufacturers. However, based on results from an informal survey of

Emergency Medicine Research Directors conducted in May 1994 and again in December 1994, there may be a substantial number of single investigator/single institution studies that will also involve waiver of consent. The comment, thus, concluded that the agency had underestimated the total number of studies that will be advanced for consideration of a waiver of consent.

This comment is correct; the agency did not consider single-investigator/single-institution studies. In response to this comment, the agency has estimated that there will be approximately 25 single-institution studies requiring an IDE and 50 single-institution studies requiring an IND annually. This paperwork section has been revised accordingly.

For Protection of Human Subjects—Recordkeeping Requirements for IRB's under OMB Control No. 0910-0130, FDA has calculated the existing recordkeeping burden on IRB's required by § 56.115 based on the estimated number of IRB's and the estimated annual number of hours each IRB spends in recordkeeping activities. FDA does not believe that this rule will increase the number of IRB's. However, the agency estimates that the number of hours for recordkeeping related to studies that propose to invoke this exception from informed consent will increase for an estimated 275 IRB's by 5 annual hours per record-keeper. This will change the estimated recordkeeper burden from 65 to 70 hours annually for these estimated 275 IRB's.

The newly redesignated and revised § 56.109(e) proposes to require that an IRB notify in writing the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. In accord with the Paperwork Reduction Act of 1995, the agency discloses that this rule requires this third party notification.

For Investigational New Drug Application under OMB Control No. 0910-0014, the agency estimates that sponsors will submit an average of 20 studies a year, with an average of 20 clinical investigators each, that propose to invoke this exception from informed consent and that sponsor-investigators will submit an average of 50 studies a year. Currently, the agency estimates the reporting requirements contained in part 312 (21 CFR 312) to average 123.34 hours per respondent annually. Reporting requirements are contained in the following sections of part 312: 312.7, 312.10, 312.23, 312.30, 312.31, 312.32, 312.33, 312.35, 312.36, 312.38, 312.41,

312.44(c)(d), 312.45, 312.47, 312.53, 312.55, 312.56, 312.58, 312.64, 312.66, 312.70, 312.83, 312.85, 312.110, 312.120(b), 312.120(c)(3), 312.140, and 312.145. FDA estimates that respondents will increase by 450 annually, resulting in an increase of 55,503 hours over that currently estimated. The reporting burden for respondents will, as a result, increase from an estimated 3,926,308 hours annually to 3,971,811 hours annually.

New § 312.54(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the clinical investigation or a substantially equivalent investigation, and other IRB's that are asked to review the investigation or a substantially equivalent investigation. In accord with the Paperwork Reduction Act of 1995, the agency discloses that this rule requires this third party notification.

For recordkeeping, under § 312.52, 312.57, 312.59, 312.62(a), 312.62(b), 312.62(c), 312.160(a) and (c), the agency estimated that an average of 165.13 hours were spent per respondent. For the estimated additional 450 recordkeeping respondents invoking this rule, this would result in approximately 74,309 hours annually. The recordkeeping burden for respondents will, as a result, increase from an estimated 2,244,090 hours annually to 2,318,399 hours annually.

For Investigational Devices Exemption Reports and Records under OMB Control No. 0910-0078, the agency estimates that 35 studies proposing to invoke this exception will be submitted to the agency annually. The number of studies upon which the current paperwork reporting burden is estimated (§ 812.20, 812.25, 812.27, 812.35, and 812.150) may, therefore, increase from 244 original submissions to 279 original submissions, increasing the number of hours by 2,800 for respondents (estimated at 80 hours per submission), from a total of 19,520 to 22,320 hours annually.

New § 812.47(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the clinical

investigation or a substantially equivalent investigation, and other IRB's that are asked to review the investigation or a substantially equivalent investigation. In accord with the Paperwork Reduction Act of 1995, the agency discloses that this rule requires this third party notification.

The number of recordkeepers, under §§ 812.43 and 812.140, is currently estimated at 700; this number is not expected to change. The estimated number of annual hours for recordkeeping requirements is expected to increase by 350 hours. The agency had estimated that original submissions require 10 hours annually of recordkeeping per submission; recordkeeping related to studies invoking this rule are expected to increase the submissions from 244 to a total of 279.

As required by section 3507(d) of the Paperwork Reduction Act of 1995, FDA has submitted a copy of this rule to OMB for its review of these previously approved information collection requirements. The agency solicited comments on the information collection requirements in order to: (1) Evaluate whether the collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the collection of information, including the validity of the methodology and assumptions used; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 50, 56, 312, 314, 601, 812, and 814 are amended as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 379e, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

2. Section 50.3 is amended by adding a new paragraph (n) to read as follows:

§ 50.3 Definitions.

* * * * *

(n) *Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

3. Section 50.24 is added to subpart B to read as follows:

§ 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not

otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the

investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with § 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially

equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

PART 56—INSTITUTIONAL REVIEW BOARDS

4. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

5. Section 56.109 is amended by revising paragraph (c), by redesignating paragraphs (d) and (e) as paragraphs (e) and (f), by adding two new sentences to the end of newly redesignated paragraph (e), and by adding new paragraphs (d) and (g) to read as follows:

§ 56.109 IRB review of research.

* * * * *

(c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) * * * For investigations involving an exception to informed consent under § 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

* * * * *

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

6. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec 351 of the Public Health Service Act (42 U.S.C. 262).

7. Section 312.2 is amended by adding paragraph (b)(6) to read as follows:

§ 312.2 Applicability.

* * * * *

(b) * * *
(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

* * * * *

8. Section 312.20 is amended by adding new paragraph (c) to read as follows:

§ 312.20 Requirement for an IND.

* * * * *

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide such written authorization 30 days after FDA receives the IND or earlier.

9. Section 312.23 is amended by adding new paragraph (f) to read as follows:

§ 312.23 IND content and format.

* * * * *

(f) *Identification of exception from informed consent.* If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24 of this chapter.

10. Section 312.30 is amended by adding a new sentence to the end of the introductory text to read as follows:

§ 312.30 Protocol amendments.

* * * Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

11. Section 312.42 is amended by adding new paragraph (b)(5) to read as follows:

§ 312.42 Clinical holds and requests for modification.

(b) * * *
(5) *Clinical hold of any investigation involving an exception from informed consent under § 50.24 of this chapter.* FDA may place a proposed or ongoing investigation involving an exception from informed consent under § 50.24 of this chapter on clinical hold if it is determined that:

- (i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or
- (ii) The pertinent criteria in § 50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

12. New section 312.54 is added to subpart D to read as follows:

§ 312.54 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under § 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

13. Section 312.60 is amended by revising the second and third sentences in the text as follows:

§ 312.60 General responsibilities of investigators.

* * * An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§ 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

14. Section 312.130 is amended by adding a new paragraph (d) to read as follows:

§ 312.130 Availability for public disclosure of data and information in an IND.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under § 50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, shall submit a request under the Freedom of Information Act.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

15. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

16. Section 314.430 is amended by redesignating paragraph (d) as paragraph (d)(1) and by adding new paragraph (d)(2) to read as follows:

§ 314.430 Availability for public disclosure of data and information in an application or abbreviated application.

(d)(1) * * *
(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the investigational new drug application that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed

consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

PART 601—LICENSING

17. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513-516, 518-520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2-12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451-1461).

18. Section 601.51 is amended by redesignating paragraph (d) as paragraph (d)(1) and by adding new paragraph (d)(2) to read as follows:

§ 601.51 Confidentiality of data and information in applications for establishment and product licenses.

(d)(1) * * *
(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IND that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

19. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 702, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

20. Section 812.20 is amended by revising paragraph (a)(1) and adding new paragraph (a)(4) to read as follows:

§ 812.20 Application.

(a) *Submission.* (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under § 50.24 of this chapter, or if FDA

notifies the sponsor that an application is required for an investigation.

* * * * *

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide such written authorization 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24 of this chapter.

* * * * *

20. Section 812.35 is amended by adding a new sentence to the end of paragraph (a) to read as follows:

§ 812.35 Supplemental applications.

(a) * * * Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IDE for such investigation.

* * * * *

21. Section 812.38 is amended by adding a new paragraph (b)(4) to read as follows:

§ 812.38 Confidentiality of data and information.

* * * * *

(b) * * *
(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

* * * * *

22. New section 812.47 is added to subpart C to read as follows:

§ 812.47 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under § 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor

shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, copies of the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA investigators who are asked to participate in this or a substantially equivalent clinical investigation and other IRB's that are asked to review this or a substantially equivalent investigation.

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

23. The authority citation for 21 CFR part 814 is revised to read as follows:

Authority: Secs. 501, 502, 503, 510, 513-520, 701, 702, 703, 704, 705, 708, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c-360j, 371, 372, 373, 374, 375, 379, 379e, 381).

24. Section 814.9 is amended by redesignating paragraph (d) as paragraph (d)(1) and by adding new paragraph (d)(2) to read as follows

§ 814.9 Confidentiality of data and information in a premarket application (PMA) file.

* * * * *

(d)(1) * * *

(2) Notwithstanding paragraph (d)(1) of this section, FDA will make available to the public upon request the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857, for investigations involving an exception from informed consent under § 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

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Dated: July 17, 1996.
David A. Kessler,
Commissioner of Food and Drugs.

Donna E. Shalala,
Secretary of Health and Human Services.
[FR Doc. 96-24967 Filed 9-26-96; 8:59 am]
BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

Waiver of Informed Consent Requirements in Certain Emergency Research

AGENCY: National Institutes of Health, HHS.

ACTION: Waiver.

SUMMARY: The Department of Health and Human Services (HHS) is announcing the waiver of the applicability of the title 45 CFR part 46 (protection of human subjects) requirement for obtaining and documenting informed consent, for a strictly limited class of research involving activities which may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. However, because of special regulatory limitations relating to research involving prisoners (subpart C of 45 CFR part 46) and research involving fetuses, pregnant women, and human in vitro fertilization (subpart B of 45 CFR part 46), this waiver is inapplicable to these categories of research.

EFFECTIVE DATE: November 1, 1996.

FOR FURTHER INFORMATION CONTACT: F. William Dommel, Jr., J.D. Senior Policy Advisor, Office for Protection from Research Risks, 6100 Executive Boulevard, Suite 3B01J, National Institutes of Health, MSC 7507, Rockville, MD 20892-7507. Telephone (301) 496-7005, ext. 203 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Waiver

Pursuant to Section 46.101(i) of title 45 of the Code of Federal Regulations, the Secretary of Health and Human Services (HHS) has waived the general requirements for informed consent at 45 CFR 46.116 (a) and (b), and at 46.408, to be referred to as the "Emergency Research Consent Waiver," for a class of research consisting of activities¹, each of which have met the following strictly limited conditions detailed under either (a) or (b) below:

¹ Because of special regulatory limitations relating to research involving prisoners (subpart C of 45 CFR part 46), and research involving fetuses, pregnant women, and human in vitro fertilization (subpart B of 45 CFR part 46), this waiver is inapplicable to these categories of research.