

## INFORMATION SHEETS

### Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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## Exception from Informed Consent For Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble

The federal regulations for the protection of human subjects in research require informed consent, with a few narrow exceptions. Following industry-FDA meetings (1993); a Congressional hearing (May 1994); a Coalition-conference of academic, medical and research organizations (October 1994); and an FDA-sponsored public forum (January 1995), FDA published in the *Federal Register* in September 1995, [60 FR 49086] a proposal to amend its regulations to permit a limited class of research in emergency settings without consent. Following a careful review of the comments received on the proposal, a final regulation was published in the *Federal Register* on October 2, 1996, [61 FR 51498]. The Department of Health and Human Services published, in the same issue, its waiver criteria which match the FDA requirements [61 FR 51531]. These documents establish a single standard for this class of research.

The new FDA regulation (21 CFR 50.24) provides a narrow exception to the requirement for 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. The intent of the new regulation is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies.

FDA recognizes that persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. FDA recognizes that the lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and

operation of this research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by an Institutional Review Board (IRB).

The regulation specifically requires 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" (Sec. 50.24(a)). This requirement is similar to 21 CFR 50.23 which requires an independent assessment by a physician not otherwise participating in the research when an investigational product is to be used in a life-threatening situation. Because 21 CFR 50.24 permits an exception from the requirement for informed consent for a group of subjects, the case-by-case independent determination is replaced by the general concurrence of a licensed physician. The option for use of a consultant to the IRB is to provide flexibility, for example, when the physician member(s) cannot participate in the deliberation and voting due to conflict of interest. Because the documented concurrence of the physician is required for approval of these studies, IRBs should ensure that meeting minutes specifically record this affirmative vote.

[Note: The numbering system used below follows the regulation numbers. The regulatory language is in italics. Readers are referred to the full text of the regulation and the preamble for additional guidance.]

According to 21 CFR 50.24, the IRB must find and document each of the following. It is clear from the regulations's wording that it is the IRB's responsibility to make decisions as to whether the criteria of the rule are met.

50.24(a)(1) *The human subjects are in a life-threatening situation,*

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 Sec. 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.

*available treatments are unproven or unsatisfactory, and*

"Clinical equipoise" must exist. "When 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." (60 FR 49086 at 49093, September 21, 1995.)

*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.*

Although the regulation specifically references placebo controlled trials, this was done to indicate that such trials may be conducted when appropriate. Other controls, e.g, active controls and historical controls, may also be used when they are appropriate and adequate to the task of providing evidence that the drug or device will have the effect claimed. 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.

*(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;*

Subjects do not have to be comatose, but the medical condition under study must prevent obtaining valid informed consent. 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. IRBs also 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.

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

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.

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

If an IRB determines that it is not appropriate to waive the requirement for informed consent because there is a reasonable way to identify prospectively the individuals likely to become eligible for the study, then this exception would not apply. In that case, only those subjects with the condition who gave prior consent may be enrolled in the study. Those individuals who either did not make a decision or who refused participation would be excluded from participation in the study. While an exception would not be allowed under this rule, the individual exception allowed under 21 CFR 50.23 might be applicable in some circumstances.

*(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.*

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.

*(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.*

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.

*(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 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.*

IRBs need to be aware of state and local laws. Some states have laws which prohibit entry of subjects into research without their express consent. This new rule does not preempt state/or local law.

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. 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.

*(7) Additional protections of the rights and welfare of 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*

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), IRBs 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.

*(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;*

It is the IRB's responsibility to determine the information to be disclosed. 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 IRB should consider how best to publicly disclose, prior to 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 the 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.

*(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;*

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, a publication may need to be supplemented by additional information. The agency has modified Sec. 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. 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.

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

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. 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 IRBs in a written IND or IDE safety report within 10 working days after the sponsor's initial receipt of the information. (See Secs. 312.32, 312.56(d), and 812.150(b)(1)).

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.

*(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.*

See previous explanation under Sec. 50.24(a)(6).

*(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.*

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.

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 Secs. 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.

Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation (21 CFR 50.24(c)). Again, like other IRB records, these are subject to inspection and copying by FDA.

*(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 Secs. 312.30 or 812.35 of this chapter.*

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 Secs. 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.

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.

*(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 IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.*

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. The agency intends this requirement to refer to clinical investigations conducted by the same sponsor.

It is the sponsor's responsibility to determine that a study is "substantially equivalent." If 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 Sec. 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 IRBs of the institutions participating in the multicenter trial. If the change is minor, it may be eligible for expedited review under Sec. 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.