Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

DRAFT GUIDANCE

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This draft guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance applies to research studies involving FDA regulated products (drugs, biological products, and medical devices). The information provided in this guidance is intended to assist sponsors, clinical investigators, and Institutional Review Boards (IRBs) in (1) the development and conduct of research in emergency settings when an exception from the informed consent requirements is requested under Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24) and (2) understanding their responsibilities for communicating with, and submitting information to, FDA.

The regulations in 21 CFR 50.24, and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provide an exception from the requirement to obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in a clinical investigation. The exception applies to emergency research for which, among other things, (1) an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)[2] is required, (2) that involves human subjects who have a life-threatening medical condition (for which available treatments are unproven or unsatisfactory), (3) that involves subjects who, because of their condition (e.g., unconsciousness) cannot give informed consent, and (4) where, to be effective, the intervention must be administered before informed consent from the subjects' legally authorized representative is feasible. Studies involving an exception from the informed consent requirements may proceed only after a sponsor has received prior

[1] This guidance has been prepared by the Good Clinical Practice Program in the Office of Science and Health Coordination, Office of the Commissioner (OC), Food and Drug Administration (FDA), in consultation with the FDA's Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Drug Evaluation and Research, and the Office of Regulatory Affairs.

[2] Sponsors should contact FDA if they have questions as to whether an IND or IDE is needed. Points of contact are listed in section "XI. For Further Information".

written authorization from FDA[3], and the IRB has found and documented that specific conditions have been met.[4]

The regulations for emergency research contain specific human subject protection requirements that are in addition to those found in other sections of 21 CFR Parts 50, and 21 CFR 56, 312 and 812. Among these requirements are the need for consultation with representatives of the community(ies) in which the research will take place and from which the subjects will be drawn, public disclosure of information before the start of the study and following its completion, a commitment by the investigator to make efforts to contact a family member to determine whether the family member objects to the subject's participation, and establishment of an independent Data Monitoring Committee (DMC). These additional requirements are necessary because the emergency research permitted under 21 CFR 50.24 involves a particularly vulnerable population: persons with life-threatening conditions who can neither give informed consent nor actively refuse enrollment. This lack of autonomy creates a special need for FDA, sponsors, IRBs, and clinical investigators to work closely together to protect the interests of this vulnerable population of subjects. At the same time, FDA needs to consider the unmet medical needs of such subjects and the potential for them to benefit from new therapies for such conditions.

The emergency research regulations became effective November 1, 1996[5]. Since that date, FDA has determined that guidance is needed to assist sponsors, IRBs, and clinical investigators in interpreting and complying with these regulations, particularly in the areas of planning and conducting community consultation and public disclosure activities, and the establishment of informed consent procedures to be used when feasible. This document also provides guidance related to other aspects of the emergency research regulations, including the need for the concurrence of a licensed physician, use of data monitoring committees, use of independent IRBs, and the documentation of efforts to contact a subject's legally authorized representative or family member regarding the subject's participation in the study.

A separate IND or IDE is required for each study protocol because, under 21 CFR 50.24, there are special requirements a sponsor must fulfill and that FDA must review to allow the study to

[3] 21 CFR 312.20(c) and 21 CFR 812.20(a)(4)(i).

[4] Section 50.24 is not intended to preempt any applicable Federal, State, or local laws requiring additional information to be disclosed for informed consent to be legally effective. See 21 CFR 50.25(c). We strongly recommend, therefore, that those conducting emergency research be familiar with the laws of the specific states in which the research will be conducted**.** 61 Fed. Reg. 51498, 51502 (Oct. 2, 1996) (Comment #10).

[5] The Secretary of Health and Human Services published a waiver of the general requirements for informed consent at 45 CFR 46.116(a) and (b), and at 46.408, for emergency research if (a) the IRB responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented (1) that the research activity is subject to regulations codified by the FDA at Title 21 CFR Part 50, and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and (2) that the requirements for exception from informed consent for emergency research detailed in 21 CFR 50.24 have been met; OR (b) the IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has found and documented that the research is not subject to regulations codified by the FDA at Title 21 CFR Part 50 and found and documented and reported that conditions for emergency research contained in the Secretarial waiver document have been met. 61 Fed. Reg. at 51531.

proceed. When appropriate, FDA will place a proposed or ongoing emergency research investigation IND (or study site) on clinical hold (1) if any of the conditions in 21 CFR 312.42(b)(1) or (b)(2) apply; or (2) if the pertinent criteria in 21 CFR 50.24 for such an investigation to begin or continue are not met. FDA may disapprove or withdraw approval of an IDE under 21 CFR 812.30 for failure to comply with "any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA."

The exception from the informed consent requirements contained in section 50.24 and described in this guidance also applies to *in vitro* diagnostic device (IVD) studies that meet all of the requirements of this section. IVD studies falling within the scope of section 50.24 would include, for example, studies in which diagnosis of a life-threatening condition cannot be confirmed by an approved product or well-established procedure (e.g., research involving an investigational test for a neurotoxin that when inhaled or in contact with skin, can cause patients to become sick within minutes and at high doses, to lose consciousness, develop seizures and die). The regulation's use of language usually associated with therapeutic products does not exclude IVDs because the administration of therapy in a life-threatening situation can depend upon a diagnostic intervention. Moreover, nothing in the scope and definitions sections of Part 50 suggests that IVDs are excluded from Part 50 regulations. Sponsors should contact the agency if they have questions as to whether a particular IVD study may be conducted under this section.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

II. STUDY DESIGN

Prospect of Direct Benefit

Under 21 CFR 50.24(a)(3), the IRB must find and document that participation in emergency research studies holds out the prospect of direct benefit to the subjects because (1) the subjects are in a life-threatening situation that necessitates intervention; (2) appropriate animal and other preclinical studies support the potential for the intervention to provide a direct benefit; and (3) the 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.

Trials that have morbidity endpoints, rather than mortality endpoints can meet the requirements of 21 CFR 50.24(a)(3) if subjects are at risk of death from the condition and severe morbidity that is closely associated with mortality is being evaluated. For example, patients with stroke or head injury are at risk of both death and severe disability. A study of an intervention to improve stroke outcome would always consider survival, but would also closely examine functional status, which might be the primary endpoint of the trial. 61 Fed. Reg. at 51508 (Comment #38). Similarly, a study intended to provide improved treatment of status epilepticus, a life-threatening

condition, might focus on reduced time to seizure control, a benefit likely to affect survival, even if it were not of sufficient size to show improved survival. FDA will consider all such studies on a case by case basis.

Practicability

An important consideration for study design is whether the trial could be practicably carried out without the waiver from informed consent requirements (21 CFR 50.24(a)(4)). By practicable, the agency means, for example, (1) that results obtained in consenting subjects would be expected to apply to subjects who are unable to provide consent, or (2) that the research would not be unduly delayed by restricting it to consenting subjects. In the first example, if the research can be carried out in subjects who can give consent (e.g., people with a stroke who are not comatose), and the results can be generalized to the subjects who cannot give consent (e.g., comatose patients), then the study would not meet the requirements of 21 CFR 50.24. It may not, however, be reasonable to extrapolate results from the less ill population. Subjects who are able to provide consent may have better prospects for full recovery than subjects who are unable to consent, or may be less susceptible to the risks of the treatment. In the second example, it might be possible to obtain consent in advance from a patient who does not have the condition that will be treated, but who suffers from a particular disease or condition that places him/her at an extremely high risk for the event to be treated (e.g., surgical patients at high risk for intra-operative stroke, cardiac patients at high risk for cardiac arrest, already hospitalized and acutely ill patients). On the other hand, even if the population at risk can be identified (e.g., cardiac patients entering a hospital), it may be impracticable to obtain consent from all of them because the event (e.g., a specific life-threatening cardiac arrhythmia) may only occur in a tiny fraction of those patients.

Subject Exclusion

Study protocols may describe situations in which emergency care personnel could reasonably infer that some incapacitated individuals would not agree to participate in a research study, even if the individuals meet the inclusion criteria. For example, members of some religious groups object to blood transfusions and other medical interventions. The clinical investigation should provide that first responders examine, as time permits, easily accessible sources of information, such as an individual's medical identification bracelets or necklaces, for evidence that may be related to that individual's willingness to participate in research.

Study Design

The regulations for emergency research (21 CFR 50.24) do not limit study designs for conducting emergency research; the study design should be adequate to the task of evaluating whether the investigational drug or device has the hypothesized effect. FDA advises study sponsors to consult with the appropriate FDA reviewing office or division if they have questions about specific study designs or whether conducting a study under 21 CFR 50.24 is appropriate. Specific contact information is provided in section "XI. For Further Information".

Placebo-controlled trials may be conducted under this emergency research provision, when appropriate (21 CFR 50.24(a)(1)). In virtually all cases, when a placebo is used, standard care (if any) would be given to all subjects, with subjects randomized additionally to receive either a test treatment or a placebo. An exception to this would be the situation in which the study objective is to determine whether some aspect of the standard treatment is in fact useful. In that case, there would be a group that does not receive that aspect of the standard treatment. Sponsors designing trials that include subjects who receive neither some aspect of the standard treatment nor a test article should provide a sound rationale for this type of study design. Choosing an appropriate design for these studies may be particularly challenging. FDA recommends that sponsors consult with the appropriate FDA office or division about such studies.

III. THERAPEUTIC WINDOW

Definition

The therapeutic window for an investigational drug, biologic, or device is the time period, based on available scientific evidence, during which the test article must be administered to have its potential clinical effect. For investigations of IVDs that meet the criteria for emergency research, the therapeutic window is the time period, based on available scientific evidence, during which diagnosis must occur to allow administration of appropriate therapy.

Therapeutic Window Rationale

The therapeutic window cannot be fully known until the relationship between time of treatment and treatment outcome is formally studied. Nevertheless, the sponsor must use available data (e.g., pathophysiologic data, animal data) to identify, to the extent possible, the therapeutic window (21 CFR 50.24(a)(5)). The therapeutic window should be specified in the study protocol, as well as how this relates to the amount of time to be devoted to seeking informed consent, as explained below.

Therapeutic Window for *InVitro* Dianostic Device (IVD) Studies

For IVD studies that meet the criteria for emergency research, the therapeutic window is the time period, based on available scientific evidence, during which diagnosis must occur to allow administration of appropriate therapy.

In practice, the therapeutic window may be determined by the characteristics of the investigational IVD or by the nature of the potential therapeutic intervention(s). For example, if available scientific evidence suggests that an IVD might reasonably produce accurate diagnostic results to allow administration of appropriate therapy only when administered within a specified interval of time, the therapeutic window would be that specified interval. On the other hand, if the therapy appropriate for a particular diagnostic outcome must be administered within a particular interval, the therapeutic window would be that interval minus the amount of time

necessary to administer and receive results from the IVD. Where the effectiveness of both the investigational IVD and the appropriate therapy are contingent upon administration within specific time intervals, the therapeutic window is the shortest interval during which the IVD results would render a diagnosis AND therapy must be administered.

Contact of Family Members

FDA does not expect that attempts to contact a legally authorized representative or a family member (if no legally authorized representative is available) must continue until the entire therapeutic window is exhausted before the test article may be administered. It would ordinarily be expected that the potential benefit of the test article will decrease as the delay in administering the test article increases. The effect of delaying administration of the test article should be taken into account when determining the portion of the therapeutic window to be devoted to seeking informed consent from a legally authorized representative or providing the opportunity for a family member to object to the subject's participation.

The IRB must review the proposed plan and procedures for attempting to contact the legally authorized representative or family member and determine whether the specified period of time for making these attempts, if any, before the test article may be administered, is appropriate (21 CFR 50.24(a)(5) and (6)). See section "IX. Contact of Legally Authorized Representatives or Family Members" for more detail.

IV. IRB RESPONSIBILITIES

General

IRB Role in Reviewing Emergency Research

The conduct of emergency research poses the unique challenges of dealing with a maximally vulnerable population, i.e., a population with no control over what happens to them and no capacity to consent, in a setting where the emergency circumstances leave inadequate opportunity to obtain consent from each subject’s legally authorized representative. To address the ethical concerns raised by conducting research on non-consenting individuals, 21 CFR 50.24 places additional responsibilities on all parties conducting or reviewing such research, including sponsors, clinical investigators, and IRBs.

Under 21 CFR 56.109, an IRB must review, and has authority to approve, require modifications in, or disapprove a proposed clinical investigation. For emergency research under 21 CFR 50.24, the IRB also must evaluate materials to determine whether the investigation satisfies the criteria in 21 CFR 50.24(a)(1) through (7) and determine whether it is appropriate to proceed under this section.

For example, IRBs are expected to review plans for community consultation and public disclosure. Community consultation activities are designed to help ensure that the communities in which the emergency research will be conducted and from which subjects will be drawn are

adequately informed about the risks and expected benefits of the research and are given the opportunity to ask questions about it as well as express their views prior to the IRB making a determination about the research. In reviewing community consultation activities, IRBs will need to exercise judgment in determining whether these activities are adequately designed to reach the broader communities identified in the investigational plan. In some cases, at the discretion of the IRB, IRB members may wish to attend and/or actively participate in various community consultation activities to hear firsthand the views of these communities if this would help the IRB understand and be sensitive to community attitudes (21 CFR 56.107(a)).

In addition, under 21 CFR 50.24(b), the IRB must ensure that there are appropriate procedures in place to inform, at the earliest feasible opportunity, subjects or their legally authorized representatives, or family members, of the subjects' inclusion in the investigation, details about the investigation, the subject's right to discontinue participation in the research, and other information contained in the informed consent document.

Because the activities under this rule are unique to emergency research studies, below is a brief description of the responsibilities IRBs have under 21 CFR 50.24 and one possible order in which they might occur. (A sample flow chart is also provided in Appendix B.)

- The clinical investigator and/or sponsor provides to the IRB:
    - materials documenting that the criteria for the exception from informed consent requirements provided in 21 CFR 50.24(a)(1) through (4) are met;
    - the proposed investigational plan, including informed consent procedures and an informed consent document, procedures and information to be used when providing an opportunity for family members to object to a subject's enrollment and/or continued participation in the study (21 CFR 50.24(a)(6) and (7)(v));
    - the clinical investigator's commitment to attempt to contact the subject's legally authorized representative to obtain consent, or provide the subject's family member an opportunity to object, prior to administering the test article during the time allotted for this within the therapeutic window (21 CFR 50.24(a)(5));
    - procedures and information to be used to inform a subject's legally authorized representative or family members about the subject's participation in the investigation in the event of a subject's death (21 CFR 50.24(b)); and
    - plans for additional protections of the rights and welfare of the subjects, including, at least, plans for community consultation and public disclosure prior to the start of the study.

- The IRB reviews these materials and determines whether the criteria are satisfied and the research may be conducted under 21 CFR 50.24, pending consideration of the input received from community consultation activities.
- If the criteria are satisfied, the IRB reviews the community consultation plans to ensure that they are designed to reach the communities identified in the investigational plan, will adequately inform the communities about the risks and expected benefits of the research, and will provide an opportunity for community members to express their views and ask questions about the proposed research. The IRB may ask for changes to the consultation plan.

- The investigator, the sponsor, or the IRB (when the IRB has decided at its discretion to carry out community consultation activities itself) conducts the community consultation activities. Some or all of the members of the IRB may attend the consultation activities in order to hear firsthand the perspectives and concerns of the communities.
- The IRB considers community concerns about and/or objections to the research.
- Before the investigation begins, the IRB must document establishment of an independent data monitoring committee to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)).
- The IRB determines whether the proposed clinical investigation can be approved and allowed to proceed and notifies the investigators and the institution(s) in writing of its decision. The IRB promptly notifies the investigator and the sponsor in writing, including a statement of the reasons for the IRB's determination, if the IRB decides that it cannot approve the investigation because it does not meet the criteria under 21 CFR 50.24 or because of other relevant ethical concerns, and explains the reasons for its decision (21 CFR 50.24(e) and 56.109(e)).
- Prior to the start of an approved investigation, the IRB reviews the information that the investigator or sponsor will publicly disclose to assure that it will reach the broader communities involved and will adequately inform them of the plans to conduct the investigation and its risks and expected benefits.
- The IRB must find and document that the public disclosure has taken place prior to initiation of the investigation (21 CFR 50.24(a)(7)(ii) and 21 CFR 312.54).
- The IRB promptly provides to the sponsor in writing a copy of the information that has been publicly disclosed about the initiation of the study under 50.24(a)(7)(ii); (21 CFR 56.109(g)).
- After the study is completed, the IRB reviews the plans for disclosure of sufficient information to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results.
- The IRB promptly provides to the sponsor in writing a copy of the information that has been publicly disclosed about the completion of the study under 50.24(a)(7)(ii) and (iii); (21 CFR 56.109(g) and 21 CFR 312.54).
- The IRB retains records related to these studies for at least 3 years after completion of the clinical investigation and makes them accessible for inspection and copying by FDA (21 CFR 50.24(c)).

IRB Selection

FDA anticipates that emergency research usually will be performed at an institution with an IRB that has the responsibility for reviewing the study at that institution. Independent IRBs may also review emergency research studies involving an exception from the informed consent requirements. The IRBs need to be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice and therefore IRBs need to include persons knowledgeable in these areas (21 CFR 56.107). IRBs that review research under this rule need to be knowledgeable about local conditions in order to evaluate the plans for community consultation and public disclosure.

Institutional responsibility for these studies should not be delegated to another IRB unless the local IRB and the administration of the institution agree. Any agreement to allow review by a non-local IRB should be in writing. 61 Fed. Reg. at 51504 (Comment #18). Copies of any agreements should be provided to all parties involved in conducting the research (e.g., the institution, local IRB, independent or central IRB, clinical investigator(s)).

IRB Documentation

IRBs must include a summary of the discussion of controverted issues and their resolution in their written minutes (21 CFR 56.115(a)(2)). FDA anticipates that a study in which informed consent is not obtained for all subjects is by its very nature controversial. Therefore IRBs must summarize their discussions and decisions regarding the required elements for these studies (21 CFR 50.24(a)) in the IRB's written meeting minutes. For example, the IRB would document its discussion of issues raised during community consultation activities, particularly discussions of community opposition to, or concern about, the emergency research study, and how such concerns were resolved.

V. LICENSED PHYSICIAN CONCURRENCE REQUIRED FOR IRB APPROVAL OF THE RESEARCH

The IRB must have the concurrence of a licensed physician, both initially and at the time of continuing review, that the criteria of 21 CFR 50.24 are met. The licensed physician must be "a member of or consultant to the IRB and . . . not otherwise participating in the clinical investigation" (21 CFR 50.24(a)). Where the licensed physician member(s) cannot participate in the deliberation and voting for any reason, participation in the convened meeting by a licensed physician consultant would be necessary. Because the concurrence of the licensed physician member or licensed physician consultant is required for the IRB to allow these studies to proceed, IRBs should ensure that meeting minutes record the licensed physician member's affirmative vote or the licensed physician consultant's concurrence (21 CFR 50.24(a) and 56.115(a)(2)).

VI. SPONSOR RESPONSIBILITIES

In addition to sponsor responsibilities required for the conduct of all clinical trials set out in 21 CFR Parts 312 and 812, 21 CFR 50.24 creates additional responsibilities for emergency research conducted with an exception from informed consent requirements. Because the activities under this rule are unique to emergency research studies, below is a brief description of the responsibilities sponsors have under 21 CFR 50.24 and one possible order in which they might occur. (A sample flow chart is provided in Appendix B.)

- As part of the investigational plan for the study, the sponsor is responsible for defining the length of the potential therapeutic window, based on scientific evidence, during which the investigational product is to be administered to the subjects (21 CFR 50.24(a)(5)).

- The sponsor is responsible for establishing an independent data monitoring committee to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)).

- The sponsor submits the protocol to FDA in a separate IND or IDE, prominently identified in the cover sheet as involving an exception from informed consent under 21 CFR 50.24 (21 CFR 50.24(d), 21 CFR 312.23(f), 21 CFR 812.20(a)(4), 21 CFR 812.35(a)).

- The sponsor obtains FDA's written authorization that the study may proceed before initiating the study (21 CFR 312.20(c); 21 CFR 812.20(a)(4)(i)).

- The sponsor assists the clinical investigator in developing and providing to the IRB:
    - materials documenting that the criteria for the exception from informed consent provided in 21 CFR 50.24(a)(1) through (4) are met;
    - the proposed investigational plan, including informed consent procedures and an informed consent document, procedures and information to be used when providing an opportunity for family members to object to a subject's enrollment and/or continued participation in the study (21 CFR 50.24(a)(6) and (7)(v));
    - the clinical investigator's commitment to attempt to contact the subject's legally authorized representative to obtain consent, or provide the subject's family member an opportunity to object, prior to administering the test article during the time allotted for this within the therapeutic window (21 CFR 50.24(a)(5));
    - procedures and information to be used to inform a subject's legally authorized representative or family members about the subject's participation in the investigation in the event of a subject's death (21 CFR 50.24(b)); and
    - plans for community consultation and public disclosure prior to the start of the study.

- The sponsor monitors the progress of all investigations involving an exception from informed consent under 21 CFR 50.24 (21 CFR 312.54(a), 21 CFR 812.47).

- The sponsor promptly submits to the IND or IDE file (and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), identified by the IND or IDE number), the information received from the IRB(s) concerning public disclosures required by 21 CFR 50.24(a)(7)(ii) and (a)(7)(iii).(See 21 CFR 312.54(a), 21 CFR 812.47(a)).

- The sponsor promptly provides in writing to FDA, to investigators who are participating or asked to participate in the same or a substantially equivalent investigation, and to other IRBs that have or are asked to review this or a substantially equivalent investigation, information related to an IRB's determination that it cannot approve a research study under 21 CFR 50.24 (21 CFR 50.24(e), 21 CFR 312.54(b), 21 CFR 812.47(b)).

- If the IRB requires modifications in the plans for community consultation, the sponsor and the clinical investigator would need to revise the community consultation plans.

- If the IRB requires modifications in the plans for public disclosure, the sponsor and the clinical investigator would need to revise the public disclosure plans.

- The sponsor may facilitate the preparation and public disclosure of the results of the study to researchers and the community(ies) involved in the study.

VII. CLINICAL INVESTIGATOR RESPONSIBILITIES

In addition to the clinical investigator responsibilities set out in 21 CFR 312 and 812, 21 CFR 50.24 creates additional responsibilities for emergency research conducted with an exception from informed consent requirements. Because the activities under this rule are unique to emergency research studies, below is a brief description of the clinical investigators' responsibilities provided under 21 CFR 50.24 and one possible order in which they might occur. (A sample flow chart is provided in Appendix B.)

- The clinical investigator, assisted by the sponsor, provides to the IRB:
    - materials documenting that the criteria for the exception from informed consent given in 21 CFR 50.24(a)(1) through (4) are met;
    - the proposed investigational plan, including informed consent procedures and an informed consent document, procedures and information to be used when providing an opportunity for family members to object to a subject's enrollment and/or continued participation in the study (see 21 CFR 50.24(a)(6) and (7)(v));
    - the clinical investigator's commitment to attempt to contact the subject's legally authorized representative to obtain consent, or provide the subject's family member an opportunity to object, prior to administering the test article during the time allotted for this within the therapeutic window (see 21 CFR 50.24(a)(5));
    - procedures and information to be used to inform a subject's legally authorized representative or family members about the subject's participation in the investigation in the event of a subject's death (see 21 CFR 50.24(b)); and
    - plans for additional protections of the rights and welfare of subjects, including, at least, plans for community consultation and public disclosure prior to the start of the study.

- If the IRB requires modifications in the plans for community consultation, the clinical investigator and sponsor would need to revise the community consultation plans and resubmit them to the IRB for review and approval.

- If the IRB requires modifications in the plans for public disclosure, the clinical investigator and sponsor would need to revise the public disclosure plans and resubmit them to the IRB for review and approval.

- During the study, the clinical investigator attempts to contact the subject's legally authorized representative to obtain consent, or provide the subject's family member an

opportunity to object, prior to administering the test article during the time allotted for this within the therapeutic window (21 CFR 50.24(a)(5)).

- The clinical investigator summarizes the efforts to contact legally authorized representatives or provide the subjects' family members with the opportunity to object to the subject's participation within the therapeutic window. The clinical investigator makes the summaries available to the IRB at the time of continuing review (21 CFR 50.24(a)(6)).

- The investigator may contribute to describing, and to the public disclosure of, the results of the study (with other participating investigators and the sponsor), to the communities involved in the study and other researchers.

VIII. COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE - General

Under 21 CFR 50.24, the IRB must find and document that additional protections of the rights and welfare of the subjects will be provided, including, at least, community consultation and public disclosure for each emergency research protocol in which an exception from informed consent is requested. "Community consultation" differs from "public disclosure" in that the former includes discussion(s) with and by a wide group of community members and representatives, and includes the IRB's consideration of such discussions before the IRB has made a decision as to whether the research should go forward. "Public disclosure," on the other hand, is a process of providing information to the community(ies), i.e., a one way transfer of information.

Community consultation refers to ensuring that the relevant community(ies) have opportunity for input into the IRB's decision-making process before initiation of the study. There thus needs to be an opportunity for the community(ies) to understand the proposed clinical investigation and its risks and expected benefits, and to discuss the investigation. The IRB should consider this community discussion when reviewing the investigational plans.

Public disclosure refers to informing the community(ies), the public, and researchers about the study (1) prior to its commencement and (2) following its completion.

Prior to commencement of the study, there must be public disclosure (21 CFR 50.24(a)(7)(ii)) of plans for the investigation. Such disclosure should include the plans for the investigation, the investigation's risks and expected benefits, information to describe the nature and purpose of the study, and the fact that informed consent will not be obtained for most study subjects. Relevant information could be obtained from the investigator's brochure and study protocol.

Following completion of the study, sufficient information about the study results must be disclosed to the community(ies) and to other researchers. Information to be disclosed must include the demographic characteristics (age, gender, and race) of the research population (21 CFR 50.24(a)(7)(iii)). Disclosure of sufficient information for researchers may be accomplished through publication of the results, both positive and negative, of the completed investigation in a

scientific journal. Disclosure of sufficient information for the community may require additional efforts to publicize the study results. FDA encourages sponsors and clinical investigators to provide public access to as much information as possible in order to permit other researchers to assess the results of these clinical investigations and, in addition, so that subsequent studies follow productive paths.

Although FDA does not dictate who should bear the costs associated with community consultation and public disclosure, the agency anticipates that the sponsor would normally bear the costs because consultation is a requirement for conducting the research. 61 Fed. Reg. at 51515 (Comment #66).

A. COMMUNITY CONSULTATION

Before a clinical study may be initiated, the IRB must find and document that consultation has occurred with representatives of the community(ies) in which the research will take place and from which research subjects may be drawn (21 CFR 50.24(a)(7)(i) and 21 CFR 56.115(a)).

Definitions

Community consultation. Community consultation means providing the opportunity for discussions with, and soliciting opinions from, the community(ies) in which the study will take place and from which the study subjects will be drawn. These communities may not always be the same; when they are not the same, both communities should be consulted.

The **community in which the research will take place** is the geographic area, e.g., city or region, where the hospital or clinical investigator study site is located.

The **community from which subjects will be drawn** is the group of patients who share a particular characteristic (e.g., persons who are at risk for the medical condition under study, persons from multiple states served by a regional trauma center). This community may be characterized by analyzing the demographics of previous hospital patients with the medical condition under study. For example, the clinical investigator might review the hospital records of the last 50-100 patients admitted to the emergency room for the medical condition under study and tabulate characteristics (gender, age, ethnicity, geographic locale, etc.).

Timing

The IRB must find and document community consultation in order to make a decision as to whether the research should proceed (21 CFR 50.24(a)(7)(i)). FDA encourages sponsors to work with IRBs and clinical investigators in developing strategies and plans for consultation with the community(ies). Sponsors may also wish to involve community representatives, including any relevant community leaders and groups, in developing community consultation plans. A sponsor may provide to an IRB a model plan and information for use in consultation with the community, but it is the responsibility of the IRB to ensure the adequacy of the community consultation (21 CFR 50.24(a)(7)(i)).

Content

Consultation provides the opportunity for the sponsor and clinical investigator(s) to (1) inform the communities that informed consent will not be obtained for most (or all) research subjects, (2) inform the communities about all relevant aspects of the study, including its risks and expected benefits, (3) hear the perspective of the communities on the proposed research, and (4) provide information about ways in which individuals wishing to be excluded may indicate this preference. The sponsor and clinical investigator(s) may obtain relevant information for this purpose from the investigator's brochure, study protocol, and the consent form that is required to be developed for the study.

The Roles of the Sponsor, Clinical Investigator, and IRB in Community Consultation

Community consultation is a unique concept for most sponsors and clinical investigators who are conducting, and IRBs who are reviewing, emergency research. For this reason, the sponsor, clinical investigator, and IRB will need to actively consult with one another to ensure that the community consultation plans are adequate and carried out in such a way that the community understands the study, including any risks and expected benefits of the proposed clinical investigation, and has the opportunity to express any concerns.

The sponsor and clinical investigator have the primary responsibility for planning and conducting the process of community consultation, hearing the concerns, and making appropriate changes in the plans for the research.

The IRB should consider the community's opinions and concerns, and assess the adequacy of the consultation process. In addition, the IRB should incorporate the results of community consultation and discussion into the IRB's own decision making about the protocol. For this reason, the IRB may wish to directly listen to the community discussions and concerns expressed in those discussions, and not rely solely on summary documentation by the clinical investigator or feedback reported by others.

To accomplish this, the IRB should

- Review, request appropriate modifications in, and approve or disapprove the plans for community consultation.

  The IRB may decide that wider community consultation and discussion is needed to help the IRB members better understand concerns about the study raised by specific groups within the community. The IRB might ask one or more IRB staff members to attend community meetings to hear concerns, and also to explain (if necessary) the proposed exception from informed consent. The IRB could also decide to invite community representatives to participate in regular or special meetings of the IRB at which the emergency research will be discussed.

- Assess the adequacy of the community consultation.

In order to find and document that community consultation has occurred, as required in 21 CFR 50.24(a)(7)(i), the IRB should assess the methods that were used and determine whether meaningful feedback was secured from the community(ies). Low attendance at meetings does not necessarily mean that there is no interest in, or no objection to, the research by the community(ies). Rather, limited or no input from the community(ies) may mean that additional efforts should be made to reach the community(ies).

- Consider the community concerns and incorporate the feedback into its review of the protocol.

  Incorporating the results of the community consultation into the IRB's deliberations is a complex matter. There are inevitably questions of how "representative" community representatives are, how to interpret views, particularly if they differ, of the communities where the study is taking place and the community from which subjects will be drawn. Based on these discussions, the IRB could recommend limiting the pool of people from which potential subjects may be drawn, for example, if particular populations had voiced opposition to participation in the investigation, but it would be critical to determine that groups can be easily identified. In some cases, if the community raises strenuous objections and concerns, an IRB may decide that the study should not be performed in its community.

- Reflect consideration of community consultation in the IRB's written summary (21 CFR 56.115(a)(1) and (2)).

Type & Frequency of Community Consultation

The clinical investigator and sponsor share the responsibility for efforts to reach the community(ies). Sponsors and clinical investigators should provide opportunities for broad community discussion, so that representatives of the community(ies) involved in the research may discuss the proposed clinical investigation, for example, in face-to-face meetings. In conducting community consultation activities, sponsors and clinical investigators should ensure that representatives from the community(ies) involved in the research participate in the consultation process.

Sponsors, clinical investigators, and IRBs (when the IRB has decided at its discretion to carry out consultation activities itself) should use the most appropriate ways to provide for effective community consultation in a particular community setting. Standing meetings, such as local civic public forums, may be better attended because such meetings are already on community members' calendars. On the other hand, organizing special meetings specifically to discuss the research may be valuable in that such meetings may draw participation from individuals with strong interest in the research. Selecting a variety of community consultation activities will broaden the opportunity for community involvement.

When an IRB has decided, at its discretion, to carry out consultation activities itself, the IRB could 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, 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. Alternatively, the IRB could use community members as consultants to the IRB. While an IRB may appropriately decide to supplement its membership with consultants from the community, expanding the IRB membership would not by itself adequately substitute for the community consultation called for in 21 CFR 50.24(a)(7)(i); broad, public consultation with the community is needed for this type of research.

FDA recognizes that other methods to consult with the community(ies) may be appropriate in some instances, for example, the use of local radio and/or television talk shows that allow viewers to "call in" to express their views and concerns. Multiple methods may be needed in order to provide the supplemental information that the IRB needs from the community to review the research. Consultation activities should be widely advertised so that representatives of as many different groups within the community(ies) as possible are included.

The number of meetings held and the number of members of the community(ies) consulted should be based on numerous factors, including the size of the community(ies), the languages spoken within those communities, the targeted research population and its heterogeneity. FDA recognizes that each community consultation process will be unique, based on the community(ies) involved and the specific nature of the investigation. There is no single, set way to accomplish this requirement.

B. PUBLIC DISCLOSURE

Public disclosure is required (1) before the emergency research may begin and (2) after the research has been completed. The IRB must find and document that public disclosure has occurred (21 CFR 50.24(a)(7)(ii) and (iii); 21 CFR 56.115(a)).

Definition

Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware of the plans for the investigation, its risks and expected benefits (see 21 CFR 50.24(a)(7)(ii)), and the fact that the study will be conducted. Public disclosure also includes dissemination of information after the investigation is completed so that the communities and scientific researchers are aware of the study's results.

1. BEFORE THE STUDY BEGINS

Who

The IRB is responsible for finding and documenting that information about the emergency research will be publicly disclosed (21 CFR 50.24(a)(7)(ii)).

Clinical investigators and sponsors are responsible for arranging public disclosure of plans for the investigation and the investigation's risks and expected benefits. FDA encourages sponsors to work with clinical investigators and IRBs in developing model strategies and information for

public disclosure as early as possible.

When

Public disclosure must occur prior to initiation of the clinical investigation (see 21 CFR 50.24(a)(7)(ii)). In addition, the IRB may determine that it is appropriate to require additional disclosure at subsequent times, for example, if new information becomes available.

Content

In order for the community to understand the risks and expected benefits of the study, the clinical investigator and sponsor must disclose the plans for the investigation to the public (21 CFR 50.24(a)(7)(ii)). This disclosure could include information that is found in the informed consent document, the investigator's brochure, and the research protocol. Appropriate disclosure includes

- a clear statement that informed consent will not be obtained for most research subjects;
- information about the test article's use, including a balanced description of the risks and expected benefits;
- a synopsis of the research protocol and study design;
- how potential study subjects will be identified;
- the sites or institutions that will be participating in the research; and
- a description of the attempts that will be made to contact a legally authorized representative, or, if no legally authorized representative is available, a family member about the subject's participation in the study, both before and after the test article is administered.

Disclosure should also include suggestions as to how individuals who do not want to participate in the research can communicate this (e.g., by use of medical identification bracelets or necklaces).

Sponsors and clinical investigators should submit public disclosure materials to the IRB for review prior to publication and dissemination. Such review helps to ensure that the material is written in language that is understandable to the community(ies) from which research subjects are drawn and in which the research will take place, and may assist the IRBs in finding and documenting that public disclosure will occur.

How

FDA recommends that multiple forums and media resources be used to widely disseminate information about the study. For example, disclosure activities could include:

- advertisements and articles in English language, and if appropriate, foreign language, newspapers;
- information on an Internet web site;
- presentation or distribution of information at meetings of community, local government, civic, or patient advocacy groups;

- letters to local and regional community leaders and first responders (e.g., police, paramedics); announcements to local/regional hospital staff(s);
- public service announcements and interviews or discussions on "talk" radio or television programs; press conferences and briefings; and
- meetings or activities provided by hospitals' and institutions' existing community outreach programs.

FDA does not believe that the following disclosure activities, by themselves or in combination, satisfy the public disclosure requirements intended under 21 CFR 50.24: a legal notice; sending a letter to physician specialists about the study; informing staff at the hospital where the study will take place. Such activities, while useful, should be combined with other methods to ensure that public disclosure requirements are fulfilled.

Publicly Disclosed Information

The IRB must promptly provide the sponsor with a copy of the information that was publicly disclosed (e.g., copies of newspaper advertisements, tapes or transcripts of radio and television shows, minutes of community meetings) so that the sponsor is aware that such disclosure has occurred. Ordinarily, the clinical investigator would provide the information to the IRB so that the IRB is aware that disclosure has occurred. The IRB provides the information to the sponsor, who provides copies of the disclosed information to FDA (21 CFR 56.109(g), 312.54(a) and 812.47(a)). There may also be situations in which the sponsor provides the information to the IRB, at the same time that the sponsor submits the information that has been disclosed to the FDA docket.

Access to Public Disclosure Information

Upon receiving copies of the information that has been publicly disclosed from the IRB, the sponsor must submit the information to FDA, to the IND/IDE and to Dockets Management at the following address (21 CFR 312.54(a) and 21 CFR 812.47(a)):

Docket Number 95S-0158 (IND#/IDE#)
Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Telephone: (301) 827-6860
Fax: (301) 827-6870

Members of the public wishing to examine public disclosure information submitted to the docket may visit the FDA's Dockets Management Branch or request copies by sending a Freedom of Information Act request to FDA at the address shown below (21 CFR 312.130(d) and 812.38):

Food and Drug Administration

Division of Freedom of Information (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Telephone: (301) 827-6500

2. PUBLIC DISCLOSURE AFTER THE STUDY IS COMPLETED

The IRB(s) must find and document that the information to be disclosed to the community(ies) and researchers is sufficient to apprise them of the study results, including the demographic characteristics (e.g., age, sex, race) of the research population (21 CFR 50.24(a)(7)(iii)). FDA recommends that the sponsor provide the information to the IRB(s) for review prior to disclosure.

The information to be disclosed about the results of investigations conducted under 21 CFR 50.24 is also subject to the regulations regarding the promotion of investigational drugs and devices. A sponsor or investigator shall not represent in a promotional context that an investigational new drug, biologic, or device is safe or effective for the purposes for which it is under investigation, or otherwise promote the drug or device (21 CFR 312.7(a) and 812.7(a)).

Who

The sponsor is responsible for analyzing the results of the overall investigation, including the demographic characteristics of the research population, and for ensuring that these results are published (or reported).

When

Disclosure of the study results to the community(ies) should occur within a reasonable period of time following completion of the investigation. For a multi-site investigation, this ordinarily will require waiting until the data from all sites have been analyzed by the sponsor.

How

Disclosure to the Community

Sponsors and clinical investigators should use appropriate mechanisms (e.g., news articles, television or radio programs, community meetings) to provide information about the results of the research to the community(ies) in which the clinical investigation was conducted and from which research subjects were drawn.

Disclosure to Other Researchers

Disclosure to researchers of the results of studies conducted under 21 CFR 50.24 is particularly important because disclosure may prevent unnecessary duplication of studies involving

vulnerable subjects who are unable to consent. FDA encourages sponsors to choose disclosure methods that will effectively reach the research community.

Sufficient information may be contained in a scientific publication of the results of the completed investigation; it may also be communicated by other means (e.g., symposia, abstracts, posting on websites). The information disclosed should provide sufficient detail to allow a clear understanding of the study design and its results, including the demographic characteristics of the research population (21 CFR 50.24(a)(7)(iii)).

See section "VIII.B.1. Publicly Disclosed Information, Access to Public Disclosure Information" for details on submission of public disclosure information to FDA.

IX. CONTACT OF LEGALLY AUTHORIZED REPRESENTATIVES OR FAMILY MEMBERS

A. PRIOR TO ADMINISTRATION OF THE TEST ARTICLE

Commitment

For each subject unable to provide informed consent, the clinical investigator participating in emergency research must commit to attempting to seek written informed consent, if feasible, from a legally authorized representative or, if no legally authorized representative is available, to attempting to contact a family member to provide an opportunity to object to the participation of an individual, before administering the test article without informed consent (21 CFR 50.24(a)(7)(v)).

Procedures

IRBs must find and document that procedures are in place for contacting and providing information to a subject's legally authorized representative or family member within the therapeutic window or at the earliest feasible opportunity (21 CFR 50.24(a)(6) and (a)(7)(v)). FDA anticipates that procedures and information will likely parallel those approved by the IRB for use in obtaining informed consent from subjects or their legally authorized representatives. IRBs must review, approve, and document that procedures are in place to be used (1) in attempting to obtain informed consent from a legally authorized representative, and (2) if no legally authorized representative is available, in attempting to contact a family member and provide an opportunity for the family member to object, prior to enrolling a subject in the study and administering the test article (21 CFR 50.24(a)(6); see also section "III. Therapeutic Window").

Informed Consent Document

An IRB-approved informed consent document, consistent with 21 CFR 50.25, must be available. The informed consent document is to be used with subjects or their legally authorized representatives in situations where feasible (21 CFR 50.24(a)(6)). The information in the

informed consent document is also to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation. The purpose of providing this information is to ensure that the subject, legally authorized representative, or family member receives adequate information about the investigation.

Opportunity To Object

The IRB is required to find and document that procedures and information to be used to provide an opportunity for a family member to object to the subject's participation in the research are in place (21 CFR 50.24(a)(6)). FDA recommends that the informed consent document be the source of the information given to the family member.

When a legally authorized representative is available, the legally authorized representative's decision will prevail. When a legally authorized representative is unavailable, if a family member objects to an individual's participation in the study, the individual should not be entered into the study.

A family member may verbally object to an individual's participation in a study. Such objections should be documented, for example, by placing appropriate entries in the individual's medical charts. If more than one family member is present and provided with the opportunity to object to the subject's participation in the study, and they disagree, the researcher and family members would need to work out the disagreement. 61 Fed. Reg. at 51506 (Comment #25).

Summary of Contact Efforts

The clinical investigator is required to summarize the efforts made to contact a legally authorized representative or, if no legally authorized representative is available, a family member, within the therapeutic window. This summary must be provided to the IRB at the time of continuing review of the study (21 CFR 50.24(a)(5) and (a)(7)(v)).

B. AFTER ADMINISTRATION OF THE TEST ARTICLE

When

IRBs must ensure there are procedures in place to provide information about the emergency research study, at the earliest feasible opportunity, to (1) the subject, if the subject's condition permits this, (2) the subject's legally authorized representative (if the subject remains incapacitated), or (3) the subject's family member (if no legally authorized representative is available), including notice that participation in the study may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled (21 CFR 50.24(b)).

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), the subject's legal representative, or family member (e.g., if the identity of the subject is never determined). 61 Fed. Reg. at 51519 (Comment #91).

IRBs must also ensure that there are procedures in place to provide information about the study to the legally authorized representative or family member in the event of the subject's death, if feasible (21 CFR 50.24(b)). The regulations do not contain a time limit for providing this information, in order to allow consideration of the emotional condition of the family members who have just learned of the death. A hospital chaplain or social worker may be helpful in determining the appropriate time to discuss the clinical investigation.

Records

Clinical investigators must summarize efforts made within the therapeutic window to contact legally authorized representatives for consent, or in the event that a legally authorized representative is unavailable, the subject's family members to provide an opportunity to object to the subject's participation in the study. The clinical investigator must make the information available to the IRB at the time of continuing review (21 CFR 50.24(a)(5) and (a)(7)(v)). FDA suggests that clinical investigators record this information in the subjects' case histories (e.g., study records, subjects' medical records, or other files) so that it may be easily retrieved, analyzed, and reported to the IRBs, and so that it is accessible if FDA conducts an inspection.

X. DATA MONITORING COMMITTEE (DMC)

Before a study may be initiated, the IRB must find and document that an independent DMC has been established to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)).

Guidance on DMCs: For more information on the roles, responsibilities and operating procedures of Data Monitoring Committees, please see FDA's Guidance for Clinical Trial Sponsors**,** Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006 (Ref . 7). The DMC guidance represents FDA's current thinking on DMCs and their operations.

XI. FOR FURTHER INFORMATION

A. CONTACTS

Sponsors, clinical investigators, and IRBs with questions regarding policy or applications pertaining to an exception from informed consent requirements for emergency research under 21 CFR 50.24 may contact the appropriate office(s) identified on FDA's website: http://www.fda.gov/oc/gcp.

B. REFERENCES

1) Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules, 61 Fed. Reg. 51498 (Oct. 2, 1996).

2) Protection of Human Subjects; Informed Consent; Proposed Rule, 60 Fed. Reg. 49086 (Sept.

21, 1995).

3) Hearing before the Subcommittee on Regulation, Business Opportunities, and Technology, Committee on Small Business, U. S. House of Representatives, May 23, 1994.

4) Coalition Conference of Acute Resuscitation and Critical Care Researchers, Consensus (Oct. 25, 1994).

5) FDA-NIH Public Forum on Informed Consent in Clinical Research conducted in Emergency Circumstances, transcript, Jan. 9-10, 1995.

6) Implementation of Emergency Research Informed Consent Waiver Rule; Public Meeting, Sept. 29-30, 1997, Bethesda, MD.

7) Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006; available online at: http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf

8) FDA's websites:
Good Clinical Practice: http://www.fda.gov/oc/gcp
Center for Biologics Evaluation and Research (CBER): http://www.fda.gov/cber
Center for Drug Evaluation and Research (CDER): http://www.fda.gov/cder
Center for Devices and Radiological Health (CDRH): http://www.fda.gov/cdrh

APPENDIX A

DEFINITIONS

Clinical investigation. (Note: The terms research, clinical research, clinical study, study, clinical trial, trial, and clinical investigation are deemed to be synonymous for purposes of this guidance.) The term means:

For drugs/biologics: Any experiment in which a drug/biologic is administered or dispensed to, or used involving, one or more human subjects (21 CFR 312.3(b)).

For devices: Any investigation or research involving one or more subjects to determine the safety or effectiveness of a device (21 CFR 812.3(h)).

Clinical Investigator. An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of that team (21 CFR 312.3(b), 812.3(i)).

Community. A community means a group or groups of people who live and work in a particular region and who may be linked by common interests; an interacting population of different kinds of individuals constituting a society or association; or, simply an aggregation of mutually related individuals in a given location (Webster's Third New International Dictionary, c. 1971). A community may also include persons who share common experiences or conditions.

Community consultation. Community consultation means providing the opportunity for discussions with, and soliciting opinions from the community(ies) in which the study will take place and from which the study subjects will be drawn.

Data Monitoring Committee (DMC). A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of current trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. For more information on DMCs and their operation, see the Draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees" (Ref. 7, issued for public comment).

Emergency Research. A planned clinical investigation that requires prior written FDA authorization to proceed and involves subject(s) who are in a life-threatening situation for which available treatments or *in vitro* diagnostic tests are unproven or unsatisfactory.

Family member. 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 (21 CFR 50.3(n)). Definition of "legally competent" may vary by state but in general includes an age of majority and an assessment of mental capacity.

Institutional Review Board (IRB). Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such a review is to ensure the protection of the rights and welfare of the human subjects (21 CFR 56.102(g)).

Legally authorized representative. An individual or judicial or other body authorized under applicable law to give informed consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (21 CFR 50.3(m)). IRBs and clinical investigators should familiarize themselves with applicable local statutes and regulations pertaining to the definition of a legally authorized representative.

Life-threatening. Diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted. 21 CFR 50.24 applies only to life-threatening emergency situations.

Public disclosure. Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware of the plans for the investigation, its risks and expected benefits, and the fact that the study will be conducted. Public disclosure also includes dissemination of information after the investigation is completed so that the communities and scientific researchers are aware of the study's results.

Sponsor. A person who takes responsibility for and initiates a clinical investigation (21 CFR 312.3(b), 812.3(n)). A sponsor may be an individual, a company, a governmental agency, an academic institution, a private organization, etc.

Sponsor-Investigator. An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational test article is administered or dispensed (21 CFR 312.3(b), 812.3(o)). A sponsor-investigator assumes the responsibilities of both sponsors and clinical investigators.

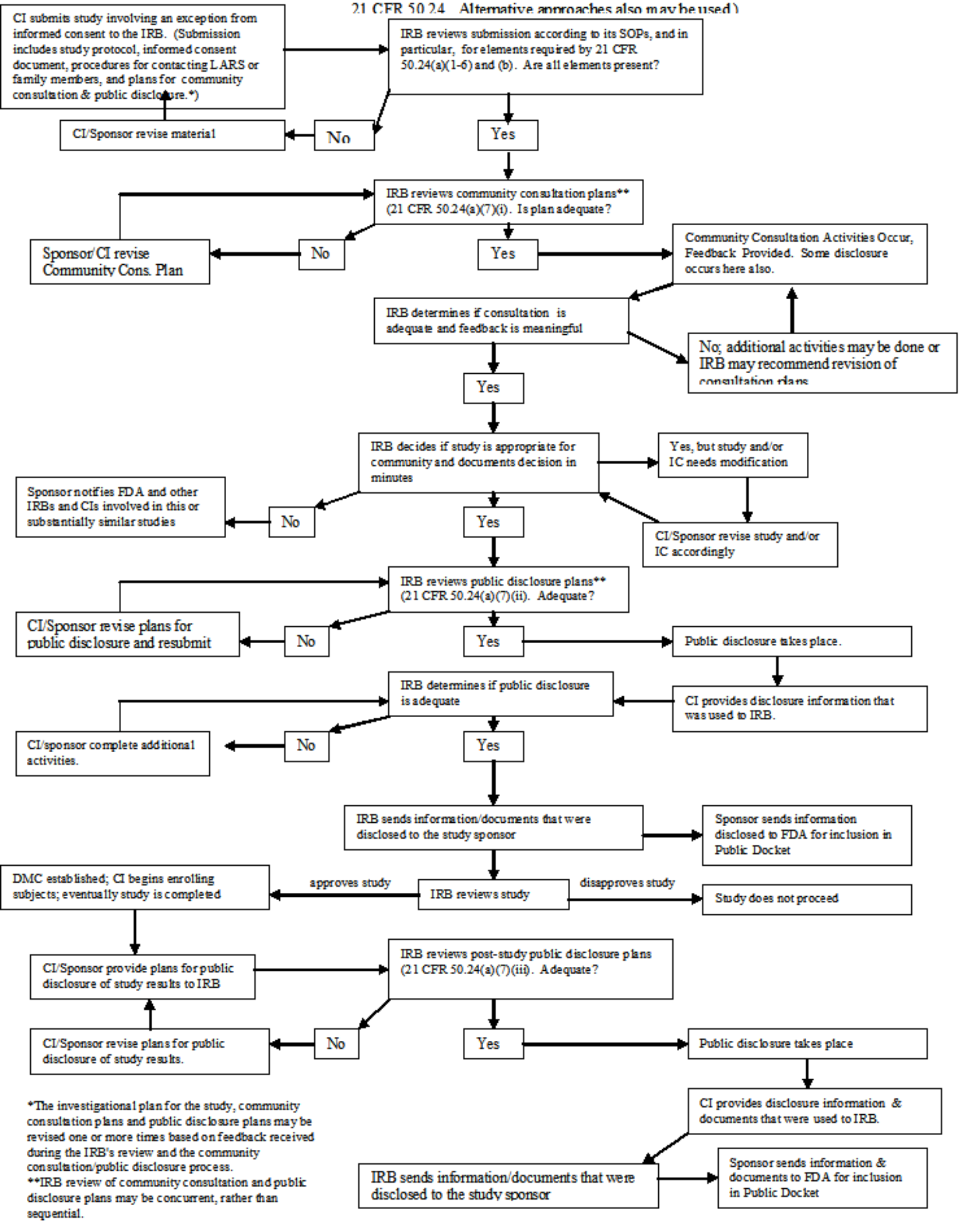
Therapeutic window. (1) The therapeutic window is the time period, based on available scientific evidence, during which administration of the test article might reasonably produce a demonstrable clinical effect. (2) For investigations of *in vitro* diagnostic devices (IVDs) that meet the criteria for emergency research, the therapeutic window is the time period, based on available scientific evidence, during which diagnosis must occur to allow administration of appropriate therapy.

Appendix B: Flow Chart

Suggested Flow Chart for 50.24 Studies

Appendix B

(This is a graphic representation of requirements for studies conducted under 21 CFR 50.24. Alternative approaches also may be used.)



*The investigational plan for the study, community consultation plans and public disclosure plans may be revised one or more times based on feedback received during the IRB's review and the community consultation/public disclosure process.

**IRB review of community consultation and public disclosure plans may be concurrent, rather than sequential.