Contains Nonbinding Recommendations

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

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Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/cder/guidance/index.htm
and/or
Office of Communication, Outreach and Development (HFM-40)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
1-800-835-4709 or 301-827-1800
and/or
Division of Small Manufacturers, International, and Consumer Assistance (HFZ-220)
Office of Communication, Education and Radiation Programs
Food and Drug Administration
Center for Devices and Radiological Health
Office of Communication, Education and Radiation Programs
10903 New Hampshire Avenue, WO66-4621
Silver Spring, MD 20993
Email: DSMICA@fda.hhs.gov
Fax: 301-847-8149
Manufacturers Assistance:1-800-638-2041 or 301-796-7100
CDRH International Staff Phone: 301-796-5680

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NOTE: FDA made the following updates to the guidance in April 2013:

- In Question #18, the phrase "unless a waiver from FDA is prospectively applied for and granted" has been deleted. FDA made this change to clarify that there are no waiver provisions applicable for 21 CFR 50.24.
- In Section XI and various other places, FDA made minor changes to clarify the provision regarding the "establishment" of an independent data safety monitoring committee (DMC). FDA interprets this regulatory provision to permit a sponsor to either establish an independent DMC or to secure the services of an already established DMC to exercise oversight of the clinical investigation. FDA is making this clarification to provide flexibility to sponsors in meeting the regulatory requirements.

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Contains Nonbinding Recommendations

Guidance for Institutional Review Boards, Clinical Investigators and Sponsors[1]
Exception from Informed Consent Requirements for Emergency Research

This 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.

This guidance is intended to assist Institutional Review Boards (IRBs), clinical investigators and sponsors in the development, conduct, and oversight of investigations to determine the safety and effectiveness of FDA regulated products (e.g., drugs, including biological drug products,[2] devices) 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). The term "emergency research" is used throughout this guidance to refer to these investigations. These investigations involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury) cannot provide informed consent. The research must have the prospect of direct benefit to the patient and must involve an investigational product that, to be effective, must be administered before informed consent from the subject or the subject's legally authorized representative can be obtained and in which there is no reasonable way to identify prospectively individuals likely to become eligible for participation. This guidance finalizes the draft guidance entitled, "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent for Emergency Research," dated July 2006 (published on August 29, 2006).[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Good Clinical Practice (OGCP) in the Office of the Commissioner (OC), Food and Drug Administration (FDA), in consultation with FDA's Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and the Center for Drug Evaluation and Research (CDER).
[2] Wherever the term "drug" is used in this guidance, it should be understood to include all drugs, including biological drug products.
[3] 71 Fed. Reg. 51143 (August 29, 2006)

I. GENERAL

1. Where are the regulations involving an exception from informed consent for emergency research studies found?

The regulations at 21 CFR 50.24 and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provide a narrow exception to the requirement that the investigator obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in emergency research. The regulations also provide additional protections for subjects enrolled in these studies. For example, the regulations require consultation with representatives of and 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. They also require public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study. As well, the regulations require that an independent data monitoring committee exercises oversight of the clinical investigation. (See Appendix A for the text of 21 CFR 50.24.)

2. Why did FDA issue the regulations at 21 CFR 50.24?

FDA issued the regulations at 21 CFR 50.24 to permit the study under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) of potential treatments or improvements in the treatment of life-threatening conditions where current treatment is unproven or unsatisfactory, in order to improve patient outcomes.

Because of ethical concerns involved in studying subjects who cannot provide consent, much of what has become standard, accepted, medical therapy for use in emergency settings has not been evaluated by adequate and well-controlled trials that demonstrate the treatment is either safe or effective. Controlled clinical trials have subsequently demonstrated that some therapies that have become standard medical practice are ineffective or even harmful. Other standard therapies, although shown to be effective in clinical trials, have significant limitations (e.g., they only work in a small percentage of those individuals who receive the therapies). FDA expects that permitting certain emergency research trials to proceed will (1) provide individuals in life-threatening situations access to potentially life-saving therapies; (2) advance knowledge through collection of information about effectiveness and safety; and (3) improve therapies used in emergency medical situations that currently have poor clinical outcomes.

3. How are emergency research studies unique?

Emergency research involves the most vulnerable population of study subjects, i.e., a population with no capacity to control what happens to them and no capacity to consent, in a setting where the emergency circumstances require prompt action and generally provide insufficient time and opportunity to locate and obtain consent from each subject’s legally authorized representative. In order to protect these vulnerable subjects, 21 CFR 50.24 places additional responsibilities on parties involved with such research, including sponsors, clinical investigators, and IRBs.

4. What are the additional responsibilities imposed on parties involved with studies conducted under 21 CFR 50.24?

These additional responsibilities include 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 try to locate the subject's legally authorized representative or contact a family member to determine whether the family member objects to the subject's participation, and study oversight by an independent data monitoring committee. (See Appendix A for the text of 21 CFR 50.24.)

5. When did the emergency research regulations take effect?

The emergency research regulations became effective November 1, 1996.[4]

6. Why did FDA issue this guidance?

FDA 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 establishing informed consent procedures to be used when feasible.[5] This document also provides guidance related to other aspects of the emergency research regulations, such as the requirement 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.

7. What must the IRB find and document in order for a study involving an exception from informed consent to proceed?

The IRB must find and document that the research involves subjects unable to consent and that the research is subject to FDA's regulations[5] and will be carried out under an FDA Investigational New Drug Application (IND) or an FDA Investigational Device Exemption (IDE). The IRB must also find and document that the requirements for exception from informed consent for emergency research detailed in 21 CFR 50.24 have been met. (See Appendix A for the text of 21 CFR 50.24.) In addition, the IRB must find that the study meets the relevant requirements of 21 CFR Parts 50 and 56.

If the IRB finds that the research is not subject to FDA's regulations, then the IRB should determine whether the research is subject to the Department of Health and Human Services' (HHS) Secretarial waiver for emergency research studies, and report this finding to HHS' Office for Human Research Protections.[6]

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[4] Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rule, 61 Fed. Reg. 51498 (Oct. 2, 1996).
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118960.htm

[5] In drafting this guidance, FDA considered comments received on two earlier published drafts of the guidance document, questions received by agency staff related to implementation of the regulations, and information presented at the October 11, 2006, public meeting on emergency research studies (Docket #2006D-0331; http://www.regulations.gov/search/Regs/home.html#home.)

[6] 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

8. Can an emergency research study be subject to both FDA's regulations at 21 CFR 50.24 and HHS regulations at 45 CFR Part 46?

Yes. If the study involves an FDA-regulated product, and is conducted or supported by HHS, both the FDA regulations and HHS human subject protection regulations apply. In order for an exception from the informed consent requirements to be granted for a study that is subject to both FDA and HHS regulations, the study may not involve pregnant women or prisoners as subjects[7], and the provisions of 21 CFR 50.24 must be satisfied. When an exception from the informed consent requirements for such a study is granted, all other applicable requirements of 21 CFR Parts 50 and 56, and 45 CFR 46 must be satisfied.

9. Does 21 CFR 50.24 pre-empt state law?

No. Section 50.24 is not intended to preempt any applicable Federal, State, or local laws.[8] Those conducting emergency research should understand their obligations under the laws of the States in which the research will be conducted.

10. Do studies conducted under 21 CFR 50.24 need a separate Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)?

Yes. If an IND or IDE already exists, protocols involving an exception to the informed consent requirement must be performed under a separate IND or IDE that clearly identifies such protocols as protocols that may include subjects who are unable to consent (21 CFR 50.24(d)). Studies involving an exception from the informed consent requirements may proceed only after a sponsor has submitted an IND or IDE[9] and received prior written authorization from FDA[10] and IRB approval (i.e., the IRB must find and document that specific conditions in the regulations have been met[11]). (See Appendix A for the text of 21 CFR 50.24.)

11. What information must be submitted to FDA for a study conducted under 21 CFR 50.24?

For an emergency research study involving an exception from informed consent, the separate IND or IDE submission should be completed as described in the applicable regulation. Information previously submitted to FDA may be incorporated by reference. The location of information incorporated by reference should be specifically identified, for example, by application number, date of submission,

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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. www.hhs.gov/ohrp/documents/100296.pdf]

[7] 61 Fed. Reg. 51531

[8] 61 Fed. Reg. 51502 (October 2, 1996, Comment #10)

[9] 21 CFR 312.2(b)(6) and 312.20(c); 21 CFR 812.20(a)(1). Sponsors should contact FDA if they have questions as to whether an IND or IDE is needed. Points of contact are listed in section "XII. For Further Information".

[10] 21 CFR 312.20(c); 21 CFR 812.20(a)(4)(i)

[11] 21 CFR 56.103(a); 21 CFR 50.24

volume, page and section. If the information was submitted by someone other than the current applicant, a letter from the person who holds the files authorizing reference to the information must be provided. In addition, the submission should address the specific requirements for studies conducted under 21 CFR 50.24 (e.g., plans for community consultation, plans for public disclosure). Sponsors should contact FDA directly if they have questions about the submission process.

12. How are emergency research studies involving investigational drugs processed?

If the protocol involves an investigational drug, the sponsor is required to submit a separate Investigational New Drug Application (IND)[12] that clearly identifies the study as including subjects who are unable to consent (21 CFR 50.24(d)). After the IND is submitted, FDA will review the study protocol under the applicable IND regulations and 21 CFR 50.24. Such a study is not permitted to proceed without the prior written authorization of FDA[13] and IRB approval (i.e., the IRB must find and document that specific conditions have been met[14]). A copy of the prior authorization from FDA may be submitted to the IRB(s) reviewing the study. (See Appendix A for the text of 21 CFR 50.24.)

13. Can Phase 1, Phase 2, and Phase 3 safety and efficacy studies proceed under 21 CFR 50.24?

The "phase" of a trial is not the focus of this regulation and there is no requirement that a study be a Phase 1, Phase 2, or Phase 3 study in order to proceed. Rather, the intervention that is being studied must hold out the prospect of direct benefit for the individual subjects. FDA expects that Phase 1 studies, including pharmacokinetic studies, would be conducted in consenting subjects and not in a trial conducted under 21 CFR 50.24, because such studies would generally not meet the criteria for the prospect of direct benefit required by 21 CFR 50.24(a)(3). To establish potential benefits, Phase 2 controlled trials in consenting subjects may be needed to explore dose response for safety or biomarkers before an investigation proceeds under 21 CFR 50.24. Sponsors should consult with FDA if there are questions as to whether a particular study meets the requirements of this regulation. (See Question 22 for discussion of appropriate endpoints of trials conducted under 21 CFR 50.24.)

14. Can feasibility/pilot trials for devices be conducted under 21 CFR 50.24?

Yes. FDA believes that feasibility/pilot studies involving devices[15] may be performed in individuals having the emergency condition provided that the study holds out the prospect of direct benefit. Sponsors should consult with FDA if there are questions as to whether a particular study meets the requirements of this regulation. (See Question 22 for discussion of endpoints of trials conducted under 21 CFR 50.24.)

15. Can emergency research studies involving investigational drugs be placed on clinical hold?

Yes. When appropriate, FDA will place a proposed or ongoing emergency research investigation IND (or study site) on clinical hold if (1) any of the conditions in 21 CFR 312.42(b)(1) or (b)(2) apply, or (2)

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[12] 21 CFR 312.20(c)
[13] 21 CFR 312.20(c)
[14] 21 CFR 56.103(a); 21 CFR 50.24
[15] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081405.htm

the pertinent criteria in 21 CFR 50.24 for such an investigation to begin or continue are not submitted or satisfied (See 21 CFR 312.42(b)(5)).

16. How are emergency research studies involving devices processed?

A sponsor is usually required to complete and submit an IDE application describing the proposed study (See 21 CFR 812.20(a)(1)). However, if the device would otherwise meet the criteria of the abbreviated requirements under 21 CFR 812.2(b), or the proposed protocol involves a device that has already been cleared or approved for marketing and is being used in accordance with its cleared/approved labeling, the sponsor or investigator should contact FDA for clarification regarding requirements for the submission of an IDE application. FDA recommends that this contact occur prior to IRB submission, particularly for multi-site studies, as this will facilitate IRB review.

If an IDE is required, FDA will review the study protocol under the IDE regulations and 21 CFR 50.24. The study is not permitted to proceed without the prior written authorization of FDA and IRB approval (i.e., the IRB must find and document that specific conditions have been met)[16]. FDA may disapprove the IDE or may withdraw approval if there is a failure to comply with any requirement of the IDE regulation, the Federal Food, Drug, and Cosmetic Act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA, including requirements related to the conduct of 50.24 studies (See 21 CFR 812.30). (See Appendix A for the text of 21 CFR 50.24.)

(See also Question 10.)

17. May studies involving in vitro diagnostic devices be conducted under 21 CFR 50.24?

Yes. An *in vitro* diagnostic device (IVD) study may be conducted provided that it meets the requirements of 21 CFR 50.24. 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. Sponsors should contact FDA if they have questions as to whether a particular IVD study may be conducted under 21 CFR 50.24.

18. Will FDA accept data from emergency research studies conducted at non-US sites?

Yes, provided appropriate regulatory requirements are satisfied. For drug/biological drug studies, if the non-U.S. sites are under an IND, all 21 CFR 50.24 requirements must be met, as well as other provisions of 21 CFR Part 312.

If the sites operate as non-IND sites, but the data are included in a marketing application, then 21 CFR 312.120 would apply. 21 CFR 312.120(a)(1)(i) "does not require informed consent in life-threatening situations when the [International Ethics Committee] reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with

[16] 21 CFR 812.20(a)(4)(i); 21 CFR 56.103(a); 21 CFR 50.24

those described in §50.23 or §50.24(a)…or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects…" FDA will accept data from non-IND emergency research studies/sites provided the emergency research is conducted in accordance with both internationally accepted standards for good clinical practice (e.g., ICH E6) and applicable national laws.

For devices, under 21 CFR 814.15(b), FDA will accept foreign studies submitted in support of a Pre-Market Approval (PMA) application if the data are valid and the investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects.

Note that some countries' laws may allow expedited appointment of legally *acceptable* representatives[17] (e.g., judge, independent physician), who can provide consent, removing the need to waive informed consent. (See 21 CFR 312.120 and 814.15 for FDA's requirements for acceptance of data from non-US studies that are *not* conducted under an IND or IDE, respectively.)

19. Must studies conducted under 21 CFR 50.24 be registered?

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[18], Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register an applicable clinical trial in the registry database, Clinicaltrials.gov,[19] and defines an "applicable clinical trial."[20] In addition, the statute describes the responsible party's obligation to report results of certain "applicable clinical trials."[21] Results must be reported if the trial conducted under 21 CFR 50.24 meets the criteria for an "applicable clinical trial" as described at ClinicalTrials.gov.

II. QUALIFICATIONS FOR A STUDY TO BE CONDUCTED UNDER 21 CFR 50.24

20. What conditions must be present for a study to be eligible to be conducted under 21 CFR 50.24?

All of the following conditions must be present:

- The human subjects are in a life-threatening situation that necessitates urgent intervention;
- Available treatments are unproven or unsatisfactory (See also Questions 23, 24, and 25);
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention;
- Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition;

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[17] FDA's regulations define the term, "legally authorized representative" as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." ICH E6 defines the term "legally *acceptable* representative" in almost identical language. See ICH E6, 1.37 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf).

[18] U.S. Public Law 110-85

[19] http://clinicaltrials.gov/

[20] http://grants.nih.gov/ClinicalTrials_fdaaa/definitions.htm

[21] http://prsinfo.clinicaltrials.gov/fdaaa.html

- The intervention must be administered before consent can be obtained from the subject's legally authorized representative;
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation;
- Participation in the research holds out the prospect of direct benefit to the subjects (See also Question 21); and
- The clinical investigation could not practicably be carried out without the waiver (See also Question 29).

(See Appendix A for the complete text of 21 CFR 50.24.)

21. What is meant by "prospect of direct benefit"?

The information from animal and preclinical studies, other clinical data (e.g., use of the product in another setting or for another diagnosis or in a different study population) or other evidence should support the potential for the investigational product to provide a direct benefit to the individual subjects.

Under 21 CFR 50.24(a)(3), the IRB must find and document that participation in an emergency research study holds out the prospect of direct benefit to the subjects because

> (1) the subjects are in a life-threatening situation that necessitates intervention;
> (2) information from appropriate animal and other preclinical studies support the potential for the intervention to provide a direct benefit to the individual subjects; 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.

22. Are trials with morbidity endpoints allowed under this regulation?

Trials that have morbidity endpoints (e.g., multiple organ failure free days), rather than mortality endpoints, can meet the requirements of 21 CFR 50.24(a)(3) if the study is evaluating severe morbidity that is closely associated with mortality, and therefore clinically relevant. 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 could also examine functional status, which might be the primary endpoint of the trial.[22] Similarly, a study intended to improve treatment of status epilepticus, a life-threatening condition, might focus on reduced time to seizure control, a benefit likely to affect survival, even if the study itself is not large enough to show improved survival.

FDA recognizes that it may be important to obtain preliminary information on dose tolerability or effect on a critical biomarker (e.g., measurement of brain infarcted area, degree and extent of acidosis) before proceeding to a study that evaluates effectiveness. Considered from the point of view of the individual study subject, the study intervention could hold out the prospect of direct benefit even if the overall study were not large enough to prove this. Such a study would be acceptable only if it could not be done in subjects capable of consenting, and all the other requirements of 21 CFR 50.24 are satisfied. In such

[22] 61 Fed. Reg. 51508 (Comment #38)

cases, FDA would expect sponsors to provide a clear rationale for conducting these studies in non-consenting subjects.

FDA will consider all proposed morbidity endpoints on a case-by-case basis. Early discussions with the appropriate FDA review divisions are encouraged.

23. What is meant by "available treatments are unproven or unsatisfactory"?

21 CFR 50.24(a)(1) requires IRBs to document that "available treatments are unproven or unsatisfactory…" For studies involving drugs, FDA has interpreted the term "available therapy" to mean therapy that is specified in the approved labeling of regulated products, with only rare exceptions. For example, a treatment that is not FDA-regulated (e.g., surgery) or a drug that is not labeled for a specific use but which is nevertheless supported by compelling evidence in the medical literature[23] may be considered an "available treatment."

For studies conducted under 21 CFR 50.24, sponsors, investigators, and IRBs should consider the following:

- What is the current "standard of care"?
- What treatments are available?
- Are available treatments (including standard of care treatments) "unproven"? (See also Question 24)
- If a product is not approved, but widely used, could a study be done to support approval?
- Are available treatments unsatisfactory, and if so, how? (See also Question 25)

24. What is meant by "unproven"?

In general, "unproven" means that there is not substantial evidence that a treatment is effective for the condition of interest. This may reflect the absence of any data or the absence of studies of acceptable quality. The term "unproven therapy" includes:

a. Treatment that is considered "standard of care" but which has never been subjected to rigorous scientific testing or submitted to FDA for approval;
b. Treatment for which there are no or insufficient clinical or pre-clinical data to support safety or efficacy of the product;
c. Treatment for which existing studies and data are insufficient to serve as the basis of approval even if the data were submitted to FDA;
d. A product that is not approved for, nor does the labeling for the product contain, the specific indication under study; and
e. An available product or therapy that is not labeled for use in a specific patient population (e.g., pediatric use).

25. What is meant by "unsatisfactory"?

[23] See Guidance for Industry, "Available Therapy" (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf) issued July 2004, by CBER and CDER.

Although a treatment may be "approved" and "available," it may be unsatisfactory. "Unsatisfactory" includes situations in which the available product or therapy is effective, but there are other drawbacks to its use, such as:

a. Safety issues (e.g., high incidence of adverse effects; exacerbation of an adverse effect for the relevant subject population);
b. Efficacy issues, including:
    - Poor survival rate;
    - The treatment is only partially effective;
    - The treatment fails to prevent a significant permanent disability;
    - Established efficacy is low;
c. The time for the treatment to be effective is too long (e.g., time to cessation of seizures);
d. The treatment has limitations related to the setting in which it is needed (e.g., should be administered in the field but needs refrigeration; is not portable; may be difficult to use (must be administered intravenously, requires surgical intervention)).

III. STUDY DESIGN

The regulations for emergency research (21 CFR 50.24) do not specify study designs for conducting emergency research. The study design should be adequate to evaluate whether the investigational drug or device has the hypothesized effect. FDA advises study sponsors to consult with the appropriate FDA review division if they have questions about specific study designs or whether conducting a study under 21 CFR 50.24 is appropriate.

26. What information should sponsors include in the proposed investigational plan (protocol) for an emergency research study?

In addition to the information that sponsors customarily provide, the sponsor should also include justification for conducting the study in subjects who cannot consent, justification as to why the investigational intervention may be better than existing, available treatment, and a description as to why existing, available treatments are unproven or unsatisfactory. In addition, the sponsor must include a rationale for selecting the therapeutic window in which the investigational product is to be used, and a description of the investigator's commitment to attempting to contact a legally authorized representative for each subject within that window of time (21 CFR 50.24(a)(5)) or to contact a family member to provide an opportunity to object to the subject's participation (21 CFR 50.24(a)(6)).

27. May placebo-controlled trials be conducted under 21 CFR 50.24?

Yes. Placebo-controlled trials may be conducted, 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 neither receive 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 the proposed study design.

28. What is a non-inferiority trial? Under what circumstances can a non-inferiority trial be conducted under 21 CFR 50.24?

A non-inferiority trial compares a test treatment to a control treatment of established effectiveness and seeks to show that the test treatment is not materially worse than or inferior to the control treatment. A non-inferiority trial seeks to show that any difference between the two treatments is small enough to allow a conclusion that the test treatment has at least some effect or, in many cases, an effect that is not significantly less than the active control. A non-inferiority trial may proceed under 21 CFR 50.24 if it meets the requirements of the regulation.

For a non-inferiority trial to be informative, there would need to be clear data about the effectiveness of the control treatment (to make the non-inferiority study interpretable) and about known safety or other problems associated with the control treatment. Non-inferiority trials are generally used in situations where a placebo-controlled trial would be unethical and where there are no data to suggest the new treatment would be more effective than the standard treatment.

A non-inferiority design trial might be used, for example, in a situation in which available treatment is effective, but is potentially damaging to other organ systems. The non-inferiority design could be used to establish effectiveness of the new therapy, while searching for a demonstrable advantage over available therapy (e.g., fewer side effects). In addition to being rigorously designed to show non-inferiority, the study should also be designed to show any safety advantage.

(For more information about clinical trial design, see ICH E10, Choice of Control Group and Related Issues in Clinical Trials.[24])

29. One of the requirements of 21 CFR 50.24 is that a study "could not be practicably carried out without the waiver" from informed consent (21 CFR 50.24(a)(4)). What does this mean?

If (1) the results obtained in consenting subjects could be generalized to subjects who are unable to provide consent, or (2) the research would not be unduly delayed by restricting it to consenting subjects, then FDA would expect the research to be performed in consenting subjects.

In the first case, 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 be reasonable, however, to extrapolate results from a 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 case, 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). However, even if the population at risk can be identified (e.g., cardiac patients entering a

[24] www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125912.pdf

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 very small fraction of those patients; therefore, subject enrollment would take too long to conduct the study in a reasonable amount of time.

Sponsors may consult with the FDA on whether an investigation meets this criterion.

30. Is it possible for researchers or first responders to identify individuals who do not want to participate?

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 plan should encourage the first responder to examine, as time permits, easily accessible sources of information, such as the medical identification bracelet, for evidence that may indicate the individual's willingness or unwillingness to participate in research. The investigational plan should also ask first responders to determine if an LAR is present, and if present and there is adequate time within the therapeutic window, to ask the legally authorized representative for consent within that window. If an LAR is not available, the first responder should ask a family member who may be present, if there is an objection to enrolling the subject in the study. (See also Questions 37, 68, and 69.)

31. May studies in pediatric subjects be conducted under 21 CFR 50.24?

Yes. Pediatric studies may be conducted under 21 CFR 50.24. In addition to the requirements of 21 CFR 50.24, the IRB must find and document that the study meets the requirements of 21 CFR 50, Subpart D.[25] 21 CFR 50.52 applies to pediatric studies that involve greater than minimal risk, but hold out the prospect of direct benefit to subjects. A study that meets the criteria in 21 CFR 50.24 would be likely to meet the criteria in 21 CFR 50.52. However, IRBs may encounter complicated issues related to emergency research studies involving pediatric subjects. 21 CFR 50.54 applies to pediatric studies that are not otherwise approvable, but which present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Section 50.54 provides a mechanism for an IRB to request a determination by the Commissioner of Food and Drugs (after consultation with a panel of pertinent experts) on whether a study is approvable.[26]

FDA recommends that community consultation and public disclosure activities for emergency research studies involving pediatric subjects include parents of children having the condition under study, and the children, too, if appropriate.

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[25] 21 CFR 50.51 applies to pediatric studies that involve no more than minimal risk. Because emergency research studies conducted under 21 CFR 50.24 would involve greater than minimal risk, 21 CFR 50.51 would not be applicable to these studies. 21 CFR 50.53 applies to pediatric studies that involve greater than minimal risk, but which provide no prospect of direct benefit; because 21 CFR 50.24 requires that the research hold out the prospect of direct benefit, studies that could be pursued under 21 CFR 50.53 would not meet the requirements of 21 CFR 50.24.

[26] See Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA under 21 CFR 50.54 (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126577.pdf).

32. What is a Special Protocol Assessment (SPA)[27]?

In general, a sponsor may request an SPA prior to initiating a study in order to address and resolve substantial scientific issues related to clinical trials, when that clinical trial's results are likely to form the primary basis of an efficacy claim in a marketing application for an investigational drug. An SPA allows FDA and the sponsor to reach agreement on the design, size, conduct, and analysis or other aspects of one or more such clinical trials.

Should it be necessary to change the protocol as a result of community consultation activities, sponsors may need to consult with FDA to determine whether principles and expectations agreed to as part of the SPA process are pertinent to the revised study.

Sponsors who wish to make non-scientific changes to a study protocol that is subject to both 21 CFR 50.24 and an SPA may do so. If a protocol is changed, the sponsor, IRB, and clinical investigator may subsequently need to conduct additional community consultation or public disclosure activities to ensure that the communities in which the research will be conducted and from which subjects will be drawn are aware of the changes.

33. Do Special Protocol Assessments (SPAs) apply to device studies?

No. However, the Center for Devices and Radiological Health (CDRH) does provide consultations with device sponsors called "early collaboration meetings." (For more information, see "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff."[28])

IV. THERAPEUTIC WINDOW

34. What is meant by the term, "therapeutic window"?

The therapeutic window for an investigational product is the time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect (diagnostic or therapeutic).

FDA recognizes that the therapeutic window for some emergency research studies may be very brief or, in some cases, almost non-existent (e.g., studies involving resuscitative devices that must be used immediately).

35. How can a sponsor determine the appropriate therapeutic window?

While the therapeutic window cannot be fully known until the relationship between time of treatment and treatment outcome is formally studied, 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

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[27] See Federal Food, Drug, and Cosmetic Act, Section 505(b)(5)(B) and (C); Guidance for Industry: Special Protocol Assessment (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080571.pdf).

[28] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

therapeutic window should be specified in the study protocol and explained in relation to the amount of time to be devoted to seeking informed consent. (See also Question 43.)

36. How does the term, "therapeutic window," apply to in vitro diagnostic 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 timely 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 <u>and</u> therapy must be administered.

37. Is it possible for an individual to indicate that he/she does not want to participate in an emergency research study?

Yes. The emergency situations to which 21 CFR 50.24 applies involve individuals who are typically unconscious or otherwise unable to communicate. There may be some cases, however, in which an individual may be conscious and able to communicate. In such cases, while full consent may be difficult or impossible, an individual may be able to indicate that he/she does not want to participate in the emergency research study, prior to administration of the test article. If the individual declines to participate in the research, his/her wishes must be honored (21 CFR 50.20). There may also be other evidence that an individual does not wish to participate in a study (e.g., medical jewelry, wallet card), an LAR at the scene who declines to provide informed consent, or a family member present at the scene who may be able to communicate a subject's unwillingness to participate in the study. (See also Questions 30, 68, and 69.)

38. What is a legally authorized representative?

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (21 CFR 50.3(l)).

39. Who may serve as a legally authorized representative (LAR)?

Some states have statutes, regulations, or common law that specifically address consent to participation in research by someone other than the subject, that is, the LAR. However, if state law does not define who is authorized to give consent on behalf of another person to participate in research, then state law governing consent for clinical procedures and/or treatments may be applicable. Institutions and IRBs

may be able to assist clinical investigators in determining if a family member is recognized under applicable state law as an LAR.

40. If an emergency research study involves pediatric subjects, who may serve as a child's legally authorized representative (LAR)?

As stated above, generally the laws of the jurisdiction in which the research takes place (e.g., State law, court order) govern who may serve as LAR. Under many states' laws, parents generally serve as LAR for their children, and in such cases would provide permission for their child's participation in a clinical investigation, including an emergency research study (21 CFR 50, Subpart D). Clinical investigators may need to verify a claim to authority (e.g., ask to see copies of court orders or other documentation) if someone other than the child's parent asserts responsibility for a child.

41. What is the purpose of contacting a subject's legally authorized representative (LAR)?

The clinical investigator must commit to attempting to contact a subject's LAR within the therapeutic window. The purpose of contacting the LAR is to ask the LAR, if feasible, for consent to enroll the subject in the study, rather than proceeding without consent (See 21 CFR 50.24(a)(5)).

42. What is the purpose of contacting a subject's family member?

If a subject's legally authorized representative is not available, the clinical investigator must attempt to contact the subject's family member (21 CFR 50.24(a)(7)(v)) in order to provide an opportunity for the family member to object to enrolling the subject in the study. If a family member is present or accompanying the subject to the emergency room, the emergency responders or investigator must ask the family member immediately if there is any objection to enrolling the subject in the study. If the family member objects, the subject must not be enrolled in the study. There is no requirement that the family member be the subject's legally authorized representative.

43. Must attempts to contact a subject's legally authorized representative or family member exhaust the entire therapeutic window before the test article may be administered to the subject?

No. FDA does not expect attempts to contact a legally authorized representative (LAR) or a family member to exhaust the entire therapeutic window 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. Thus, 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 LAR or providing the opportunity for a family member to object to the subject's participation.

Before determining that a study has met the requirements in 21 CFR 50.24, the IRB must review the proposed plan and procedures for attempting to contact the LAR or family member and determine whether the specified period of time for making these attempts, before the test article may be administered, is appropriate (21 CFR 50.24(a)(5) and (6)). (See section "X. Contact of Legally Authorized Representatives or Family Members" for more detail.)

V. IRB RESPONSIBILITIES

44. What is the IRB's role in reviewing emergency research?

Under 21 CFR 56.109, an IRB must review and have authority to approve, require modifications in, or disapprove a proposed clinical investigation. For emergency research under 21 CFR 50.24, the IRB, with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation (See also Question 51), must find and document[29] whether the investigation satisfies the criteria in 21 CFR 50.24(a)(1) through (7) and whether the investigation may be approved under this section.

For example, IRBs must review plans for community consultation and public disclosure (21 CFR 50.24(a)(7)(i), (ii), (iii)). Community consultation activities should be 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, and express their views prior to the IRB making a determination about the research.[30] 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.

Each IRB is required to "…be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects…" (21 CFR 56.107(a)). Thus, FDA recommends that IRB members attend community consultation activities to hear the views of these communities.

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, each 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, a brief description of the IRB's responsibilities under 21 CFR 50.24 and one possible order in which they might occur is provided below. (A sample flow chart is provided in Appendix C.)

45. What information should the clinical investigator or sponsor provide to the IRB related to a research protocol involving an exception from informed consent under 21 CFR 50.24?

The clinical investigator or sponsor should provide the following:

- materials documenting that the criteria for the exception from informed consent requirements for emergency research listed in 21 CFR 50.24(a)(1) through (4) are met;

[29] The determinations of the convened IRB must be documented in the IRB's written meeting minutes (21 CFR 56.115(a)(2)).
[30] Fed. Reg. 61 51514, (Comment #60)

- the clinical investigator's commitment to attempt to contact the subject's legally authorized representative (LAR) to obtain consent, or provide the subject's family member an opportunity to object, if feasible, prior to administering the test article during the time allotted for this contact, in order to obtain consent, within the therapeutic window (21 CFR 50.24(a)(5) and (7)(v));
- the proposed investigational plan, including informed consent procedures and an informed consent document, procedures and information to be used when providing an opportunity for a subject, LAR, or family member to object to a subject's enrollment and/or continued participation in the study (21 CFR 50.24(a)(6) and (7)(v));
- procedures and information to be used to inform a subject's LAR 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 (21 CFR 50.24(a)(7)).

46. What does the IRB do with the submitted information?

The IRB reviews the submitted information, determines whether the criteria under 21 CFR 50.24 and 56.111 (and Part 50, Subpart D for pediatric research) are satisfied, and determines whether the research may be approved, pending consideration of the input received from community consultation activities. Because of the complexity of these studies and the 50.24 process, more than one IRB meeting may be necessary for the IRB to complete its review. Depending on the submitted information, the community consultation, and its obligations under 21 CFR 50.24, the IRB will consider a wide variety of determinations and actions. The list below provides one example of how an IRB might review and respond to materials related to an emergency research study.[31]

- If the criteria under 21 CFR 50.24 and 56.111 (and Part 50, Subpart D for pediatric research) are satisfied, the IRB reviews the community consultation plan to ensure that it is 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 require changes to the community consultation plan (21 CFR 56.109(a)).
- The investigator and the sponsor (or the IRB where appropriate, that is, when the IRB has decided at its discretion to carry out community consultation activities itself) conduct the community consultation activities. FDA encourages IRB members to attend community consultation activities in order to hear the perspectives and concerns of the communities.
- The IRB considers concerns and objections to the research raised during community consultation activities.
- Before the investigation begins, the IRB documents that the sponsor has arranged for an independent data monitoring committee[32] to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)). (See also Question 116.)

[31] Some of the activities under this rule are unique to emergency research studies; the order in which these activities occur is not specified in the regulations and may vary.
[32] See "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees" (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf).

- 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.
- If the IRB decides that it cannot approve the investigation because it does not meet all of the criteria under 21 CFR 50.24 and 56.111 (and Part 50, Subpart D for pediatric research), or because of other relevant ethical concerns, the IRB promptly notifies the investigator and the sponsor in writing, including a statement of the reasons for the IRB's determination (21 CFR 50.24(e) and 56.109(e)).
- Prior to the initiation of an investigation, the IRB reviews the information that will be publicly disclosed to assure that the information will reach the broader communities involved and will adequately inform the affected communities of the plans to conduct the investigation and its risks and expected benefits.
- The IRB must find and document that the public disclosure will have or has taken place prior to initiation of the investigation (21 CFR 50.24(a)(7)(ii)).
- 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 21 CFR 50.24(a)(7)(ii): see 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 following completion of the study (21 CFR 50.24(a)(7)(iii); 21 CFR 56.109(g), 312.54(a) and 812.47(a)).
- 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)).

47. Is the IRB responsible only for finding and documenting that the plans for community consultation and public disclosure exist, or does the IRB have additional responsibilities for ensuring that these activities are implemented?

- The IRB must review the plans for community consultation and public disclosure before the plans are implemented (21 CFR 50.24(a)(7)(i), (ii), (iii)). FDA also expects the IRB to consider the concerns and objections raised during community consultation activities when the IRB deliberates on whether to approve, require modifications in (to secure approval) or disapprove the research activity. An IRB may decide, at its discretion, that it is appropriate for the IRB itself to carry out community consultation activities, for example, if it determines that the plans were not adequately implemented. In addition, the IRB must find and document that the public disclosure will have or has taken place prior to initiation of the investigation (21 CFR 50.24(a)(7)(ii)).

48. If an IRB determines that it needs additional input from the community about the study, what should the IRB do?

The IRB could:

- Invite members of the community from which the subjects will be drawn to an IRB meeting to discuss the study;

- Consistent with IRB membership requirements (see 21 CFR 56.107), enhance the membership of the IRB by adding members who are not affiliated with the institution and are representative of the community;

- Use community members as consultants to the IRB under 21 CFR 56.107(f). Use of consultants would not by itself adequately substitute for the community consultation called for in 21 CFR 50.24(a)(7)(i);

- Request that the sponsor and investigator conduct additional or other community consultation activities; and

- Decide, where appropriate, to conduct community consultation activities itself (21 CFR 50.24(a)(7)(i)). The IRB could use one or more of the activities listed in Question 76 (e.g., hold a public community meeting to discuss the protocol).

49. Must an emergency research study be reviewed only by IRBs that are affiliated with institutions?

No. All of the options available for IRB review of non-emergency research studies are also available for review of emergency research studies. Examples include, but are not limited to, the following:

- Emergency research may be reviewed by an IRB that is responsible for reviewing all studies at a particular institution.
- Emergency research may be reviewed by an independent (commercial) IRB.
- Emergency research may be reviewed using a centralized IRB process.[33, 34, 35]) When a centralized IRB process is used:
    - The central IRB may be responsible for reviewing all aspects of the study, including local issues.
    - Review may be shared by a local IRB and central IRB who cooperate in the review of emergency research studies. (21 CFR 56.114) For example, the central IRB may agree to be responsible for the scientific review of the study and the informed consent document; the local IRB may agree to be responsible for evaluating plans for community consultation and public disclosure.

[33] A centralized IRB review process may be helpful in multi-site trials to improve efficiency and/or consistency in the scientific review, and eliminate duplication of effort.
[34] OHRP requires cooperative agreements (i.e., any designation under the Assurance of another Institution's IRB or an independent IRB) to be documented in writing by a written agreement between the Institution and the IRB organization outlining their relationship. This requirement is derived from the provision under 45 CFR 46.103(a) which states that "Each institution engaged in research covered by this policy…shall provide written assurance satisfactory to the department or agency head." For more information about cooperative review for research covered by 45 CFR 46, see http://www.hhs.gov/ohrp/assurances/assurances_index.html.
[35] See Guidance for Industry: Using a Centralized IRB Review Process in Multi-Center Clinical Trials; http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm.

Any IRB that reviews an emergency research study must be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice; therefore the IRB needs to include persons knowledgeable in these areas (21 CFR 56.107).

The IRB that is responsible for finding and documenting that community consultation and public disclosure will take place (as required by 21 CFR 50.24(a)(7)) should be knowledgeable about local conditions in order to evaluate the community consultation and public disclosure plans. A central IRB may want to obtain input from an IRB at the institution where the research is to be conducted, to ensure that local concerns are addressed. The institution's IRB may have additional insights or knowledge about local or State laws or regulations pertaining to emergency research studies, the demographics of the area in which the study will take place, the need to translate the informed consent document, community consultation or public disclosure materials into other languages, practices of emergency medical services in the area, etc.

Responsibility for these studies should not be delegated to another IRB unless the institution agrees to the transfer. Any such agreements to allow review using a centralized IRB process or an IRB other than the institution's IRB should be in writing.[36] Copies of any agreements should be provided to all parties involved in conducting the research (e.g., the institution, the institution's IRB, the central IRB, clinical investigator(s)).

50. How should an IRB document its review of an emergency research study?

IRB meeting minutes must be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution (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. If the IRB approves the study despite the objection of some part(s) of the community, the IRB should also document this, and provide its reason(s) for doing so.

51. What is meant by "licensed physician concurrence"?

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 (21 CFR 50.24(a)). 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

[36] In the preamble to the proposed rule, FDA said that the agency anticipates that research involving an exception from informed consent will usually be performed at an institution with an IRB. However, any duly constituted IRB can ensure that the rights and welfare of research subjects are protected by fulfilling the requirements of part 56 (21 CFR part 56) and § 50.24, including § 50.24(a)(7) requiring public disclosure to and consultation with the communities from which the subjects will be drawn. FDA recognizes that independent IRBs can also review such studies, or institutions can enter into agreements to use a centralized IRB review process. Any agreement delegating review responsibilities to an independent IRB or using a centralized IRB Review process should be documented in writing. See 61 Fed. Reg. 51504 (Comment #18).

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'S RESPONSIBILITIES

52. What are the sponsor's responsibilities under 21 CFR 50.24?

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 under this exception from informed consent requirements. Below is a list of the sponsor's responsibilities under 21 CFR 50.24 and one possible order in which they might occur.[37] (A sample flow chart is provided in Appendix C.)

- As part of the investigational plan for the study, the sponsor is responsible for defining the length of the potential therapeutic window,[38] 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 using an independent data monitoring committee to exercise oversight of the clinical investigation (21 CFR 50.24(a)(7)(iv)).[39]

- The sponsor submits the protocol to FDA in a separate IND or IDE, the cover sheet of which prominently identifies the study 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 must obtain FDA's written authorization before the study may proceed (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:
    - information to document 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), and 50.24(b));
    - the clinical investigator's commitment to attempt to contact the subject's legally authorized representative (LAR) to obtain consent, or provide the subject's family

[37] Some of the activities under this rule are unique to emergency research studies; the order in which these activities occur is not specified in the regulations and may vary.
[38] For more information, see Section IV. Therapeutic Window.
[39] For more information on data monitoring committees, refer to FDA's Guidance on Establishment and Operations of Clinical Trial Data Monitoring Committees; www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf.

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) and (a)(7)(v));
  - procedures and information to be used in the event of a subject's death to inform a subject's LAR or family members about the subject's participation in the investigation (21 CFR 50.24(b));
  - plans for community consultation and public disclosure prior to the start of the study; and
  - information about opt-out mechanisms, if any are proposed by the sponsor. (See also Question 68.)

- The sponsor and clinical investigator (or, where appropriate, the IRB, when the IRB has decided at its discretion to carry out community consultation activities) conduct the community consultation activities. FDA recommends that one or more IRB members attend the community consultation activities in person (see also Question 44), but if an IRB member is not able to do so, information gleaned from the community consultation activities should be provided to the IRB. The IRB should determine how information from community consultation activities is to be provided to the IRB (e.g., oral report at IRB meeting, written report by the investigator).

- The sponsor must monitor 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 must promptly submit 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), copies of the information that was publicly disclosed prior to initiation of the clinical investigation (e.g., plans for the investigation and its risks and expected benefits); see 21 CFR 50.24(a)(7)(ii), 312.54(a), 812.47(a)). (See also Question 84.)

- The sponsor must promptly provide in writing to FDA, information related to an IRB's determination that it cannot approve a research study under 21 CFR 50.24. The sponsor must also provide this information to investigators who are participating or asked to participate in the same or a substantially equivalent investigation, and to other IRBs that have reviewed or are asked to review this or a substantially equivalent investigation (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 are responsible for revising the community consultation plans and resubmitting them for IRB review (21 CFR 56.109(a)).

- If the IRB requires modifications in the plans for public disclosure, the sponsor and the clinical investigator are responsible for revising the public disclosure plans and resubmitting them for IRB review (21 CFR 56.109(a)).

- Following completion of the study, the sponsor prepares information to apprise researchers and the community(ies) about the study, including demographic characteristics of the research population, and the study's results (21 CFR 50.24(a)(7)(iii)).

- The sponsor must promptly submit to the IND or IDE file copies of the information that was publicly disclosed. The sponsor must also submit the information to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), identified by the IND or IDE number (21 CFR 312.54(a) and 21 CFR 812.47(a)). (See also Questions 84 and 94.)

VII. CLINICAL INVESTIGATOR'S RESPONSIBILITIES

53. What are the clinical investigator's responsibilities under 21 CFR 50.24?

In addition to the clinical investigator responsibilities set forth in 21 CFR 312 and 812, 21 CFR 50.24 creates additional responsibilities for emergency research conducted with an exception from informed consent requirements. Below is a list of the clinical investigator's responsibilities under 21 CFR 50.24 and one possible order in which they might occur.[33] (A sample flow chart is provided in Appendix C.)

- 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 (21 CFR 50.24(a)(6) and (7)(v), and 50.24(b));
    - 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) and (a)7(v));
    - 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 subjects, including, at least, plans for community consultation and public disclosure prior to the start of the study.

- The investigator and sponsor (or the IRB, when the IRB has decided at its discretion to carry out community consultation activities itself) conduct the community consultation activities. IRB members should attend the community consultation activities in person, but if that is not possible, information gleaned from the community consultation activities should be provided to the IRB.

- 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.

- Prior to beginning the study, the clinical investigator should ensure that all individuals, including first responders, who will carry out study-related tasks, are informed of their obligations and associated regulatory requirements for conducting these studies. This may necessitate conducting specific training programs for first responders and site staff (for example, use of the investigational product, timing of and appropriate communication with legally authorized representatives (LARs) or family members).

- During the study, the clinical investigator examines, as time permits, easily accessible sources of information, such as the medical identification bracelet, for evidence that may indicate the individual's willingness or unwillingness to participate in research, and attempts to contact the subject's LAR to obtain consent prior to administering the test article during the time allotted for this within the therapeutic window and, if feasible, asks the LAR for consent within that window rather than proceeding without consent (21 CFR 50.24(a)(5)). If the LAR is not available, the investigator attempts to contact the subject's family member during the time allotted for this within the therapeutic window, to ask whether he or she objects to the subject's enrollment in the study (21 CFR 50.24(a)(7)(v)).

- During the study, at the earliest feasible opportunity, the clinical investigator informs the subject, the subject's LAR, or family member (1) of the subject's inclusion in the study, the details of the investigation and other information contained in the informed consent document, and (2) 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 (21 CFR 50.24(b)).

- If the subject improves, the subject is also to be informed as soon as feasible (21 CFR 50.24(b)).

- If the subject dies before a LAR or family member can be contacted, information about the clinical investigation is to be provided to the subject's LAR or family member, if feasible (21 CFR 50.24(b)).

- The clinical investigator summarizes the efforts made within the therapeutic window to contact each LAR or provide each subject's family member with the opportunity to object to the subject's participation. The clinical investigator must make the summaries available to the IRB at the time of continuing review (21 CFR 50.24(a)(6)).[40]

- Following completion of the study, the investigator may assist the sponsor with, or contribute to, preparation of information to apprise the communities and other researchers about the study, including demographic characteristics of the research population and the study's results (21 CFR 50.24(a)(7)(iii)).

VIII. COMMUNITY CONSULTATION

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, "consultation (including, where appropriate,

[40] 61 Fed. Reg. 51510

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" (community consultation; 21 CFR 50.24(a)(7)(i) and 21 CFR 56.115(a)); and public disclosure for each emergency research protocol in which an exception from informed consent is requested (21 CFR 50.24(a)(7)(i-iii)). For a multisite trial, FDA expects the sponsor and investigator to hold community consultation activities for communities at all sites.

54. What is meant by "community consultation" and what are its goals?

Community consultation means providing the opportunity for discussions with, and soliciting opinions from, the community in which the study will take place and the community 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 goals of community consultation are to:

- show respect for persons by informing the community about the study in advance;
- inform community members about the trial in advance and provide a means for affected communities to provide meaningful input to the IRB before its decision to approve, require modifications to, or disapprove the study;
- show respect for the community by allowing representatives of the community to identify potential community-level concerns and effects of the research; and
- show respect for subjects' autonomy. Respect may be shown by including in community consultation activities individuals who may have, or be at risk for, the condition under study (and thereby obtain input from a group that is expected to be similar to the eventual study subjects).

55. What is meant by "the community in which the research will be conducted"?

FDA interprets the phrase, "the community in which the research will be conducted" to mean the geographic area, e.g., hospital or other facility, or city or region, where the hospital or clinical investigator study site is located. Persons from multiple states served by a regional trauma center, emergency room staff or other health care providers affiliated with the hospital or trauma center, and regional emergency medical technicians, paramedics and first responders may also be considered part of the "community in which the research will be conducted." (See also Questions 56, 65, and 73.)

56. What is meant by "the community from which subjects will be drawn"?

FDA interprets the phrase, "the community from which subjects will be drawn" (i.e., the community at risk**)** to mean the group of patients who share a particular medical or other characteristic that increases the likelihood that they (or a family member) may be enrolled in the study. (See also Questions 55, 65, and 73.)

57. Is community consultation the same as "community consent" for the study? Is "community consent" a substitute for individual informed consent?

No. Community consultation is not the same as community consent. Community consent is the idea that a community's leaders can consent to the community's participation in a study, and thereby eliminate the need for researchers to obtain informed consent from individual subjects. Community consent is not a substitute for individual informed consent required under the IND/IDE regulations, nor can the community consent on behalf of individual members to permit their participation in a study. The usual way of respecting a person's autonomy--by directly obtaining the individual's consent—may be impossible for emergency research. Similarly, community consultation cannot substitute for individual consent, although community consultation does represent an opportunity for people situated similarly to potential study subjects to hear about the study and express views about it.

58. What should happen during community consultation?

During community consultation, the sponsor and clinical investigator(s) should

(1) inform the communities that it is proposed that informed consent will not be obtained for most (or all) research subjects, including an explanation as to why consent is not feasible (i.e., why the research is being conducted using the exception provided under 21 CFR 50.24);
(2) inform the communities about all relevant aspects of the proposed study, including its risks and expected benefits;
(3) hear and respond to the perspective of the communities on the proposed research; and
(4) provide information about ways, if any, in which individuals wishing to be excluded may indicate this preference.

59. What information should be included in community consultation?

The content and extent of community consultation activities (see below) may vary depending on what is known about the product and what is known about the risks posed by the study. When community consultation plans are being developed, the following factors should be considered:

- protocol design (e.g., whether the investigational product is substituted for or added to standard of care);
- what is known about the test article (e.g., FDA approved, available safety or toxicity information, product history including extent of use, approval in another population or for another indication, scientific evidence from other countries);
- what is known about the medical condition;
- what is known about the safety and efficacy of "standard of care" (i.e., why existing, available treatments are considered unproven or unsatisfactory);
- study population (e.g., adults vs. pediatric population);
- characteristics of the setting in which the test article will be administered (e.g., will the product first be administered in the ambulance by EMTs or in the ER, will the product be continued in the ER, what is the availability of resources, what training will be provided to personnel who will be involved with the research)
- timing of administration of the test article;
- invasiveness of procedures necessary to administer the product;
- perceived availability or acceptability of alternative treatments.

At a minimum, the content of community consultation should include:

- A summary of the research protocol, study design, and a description of the procedures to be followed, including the identification of any procedures which are experimental;
- A summary of other available treatment options and what is known about their risks and benefits;
- An estimate of how long the study will last and expected duration of the subject's participation;
- How potential study subjects will be identified;
- Information about the test article's use, including a balanced description of the risks and expected benefits and any relevant information that is known about adverse events;
- A clear statement that informed consent will not be obtained for most research subjects;
- The rationale as to why the study must be conducted using an exception from informed consent;
- A copy of the informed consent document;
- Relevant information that would be part of the informed consent process (21 CFR 50.25(a) and (b), as applicable), e.g., available treatments for the condition under study; risks/potential benefits of participating in the research; possibility that FDA might inspect the subject's records;
- A description of the therapeutic window, during which the test article must administered, and the portion of that window that will be used to contact the subject's LAR;
- A description of the attempts that will be made to contact the subject's LAR to obtain consent, or, if no LAR is available, a family member to provide an opportunity to object to the subject's enrollment in the study, both before and after the test article is administered (See Questions 38-43);
- A description of the way(s) in which an individual may express his/her desire not to participate and avoid involvement as a subject in the research (e.g., opt-out mechanisms), if any will be made available (See Questions 37 and 68);
- Reasons why community input is important;
- Known community perceptions/concerns associated with the study, product, and/or standard of care; and
- Identification of individuals to contact for more information about the study.

(See Question 81 for the contents of appropriate public disclosure.)

60. Why is community consultation important?

Community consultation helps to ensure that the community(ies) most affected by the research have an opportunity for input into the IRB's decision-making process. Community consultation provides an opportunity for the community(ies) to understand the proposed clinical investigation and its risks and expected benefits, and to discuss the investigation.

Community consultation also helps to ensure that IRBs, independent, commercial IRBs as well as those affiliated with an institution, have the means to acquire (1) knowledge of community attitudes related to the proposed research involving an exception from informed consent and (2) information on conditions

surrounding the conduct of the research. Such consultation may also strengthen community confidence in the role of the IRB and its decision-making capacity, particularly since the community discussion will be considered by the IRB when reviewing the investigational plans for the study.

61. What is meant by the phrase, "representatives of the community" (21 CFR 50.24(a)(7)(i)? Must a representative of the community be an elected official?

FDA interprets the terms "representatives of the community" to include not only elected officials, but also clergy, local community activists, leaders of advocacy organizations, tribal leaders, school officials, and other interested individuals. Although sites may wish to notify elected officials about the plans for the research, simply informing elected officials would not be sufficient to fulfill community consultation requirements of the regulations. The types and number of representatives who participate in community consultation activities may vary by study or even across sites within the same study.

It is critical that community consultation include the people who are more likely to be affected by the research and that they be appropriately consulted during community consultation so that they understand the nature of the research. Information gleaned from broad consultation with the affected communities may help the IRB in its review and deliberations related to the study.

62. How does "community consultation" differ from "public disclosure"?

FDA interprets the term "community consultation" to include 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 (i.e., two-way communication). FDA interprets the term "public disclosure," on the other hand, to be the process of providing information to the community(ies), i.e., a one way transfer of information. (See Section "IX. Public Disclosure", Question 78, for more details about "public disclosure.")

63. Who should bear the costs associated with community consultation and public disclosure activities?

Although FDA's regulations do not state who should bear the costs associated with community consultation and public disclosure, the agency anticipates that the sponsor would normally bear the costs because community consultation and public disclosure are required to conduct the research.[41]

64. May IRBs review the study protocol separately from the community consultation and public disclosure plans?

FDA does not recommend reviewing the protocol separately from the other plans. Because the protocol and plans for community consultation and public disclosure can all influence each other, IRBs should review the study protocol and community consultation and public disclosure plans as a package. The IRB may review all materials, in order to find and document that the additional protections (community consultation and public disclosure) will be conducted. When community consultation is completed, the IRB could then reexamine the protocol, and vote to approve, require modifications to, or disapprove the

[41] 61 Fed. Reg. 51515 (Comment #66)

research. (The IRB may, of course, have questions related to individual items. Because of the complexity of these studies, it may take the IRB more than one meeting to review and approve these studies.)

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 be conducted and from which research subjects may be drawn (21 CFR 50.24(a)(7)(i) and 21 CFR 56.115(a)).

65. How can clinical investigators identify who belongs to the community from which subjects will be drawn?

Clinical investigators may be able to identify or characterize the community at risk for the medical condition under study by analyzing the demographics of previous hospital patients. 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, etc.). This will also assist the investigator in identifying the target population(s) that should be included in community consultation activities. (See also Questions 55, 56, and 73.)

66. What is the IRB's role in the community consultation process?

In order to approve the research, the IRB must find and document that community consultation will be provided (including, where appropriate, consultation carried out by the IRB; 21 CFR 50.24(a)(7)(i)). 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)). Sponsors may work with clinical investigators and consult with the IRB 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 for the geographic area in which the research will take place, to ensure that the study is in compliance with State or local laws and regulations.

The IRB has discretion to determine the circumstances in which it would be appropriate for the IRB to carry out community consultation. If community consultation is carried out by the sponsor or clinical investigator, FDA encourages IRB members to attend community consultation activities in order to hear the perspectives and concerns of the communities, and to allow the IRB to consider these concerns and objections during the IRB's deliberations about the research.

(See also Question 74.)

67. Where should the sponsor and clinical investigator obtain information about the study for inclusion during community consultation?

Relevant information can be found in the study protocol, investigator's brochure, and the informed consent document.

Note that the information to be included in community consultation about 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 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)).

68. Must "opt-out" mechanisms be provided?

No. "Opt-out" mechanisms (i.e., ways for an individual to indicate a desire to not participate in research involving an exception from informed consent) are not required under 21 CFR 50.24.[42] However, individuals in the community may ask about them. Opt-out mechanisms may include, for example, providing individuals with a wallet card or medical bracelet that contains a statement that the individual does not want to participate in research.

The decision to use opt-out mechanisms is left to the discretion of the IRB, since opt-out mechanisms are not required by FDA's regulations. The IRB should determine whether it is feasible to provide individuals in the community with an opt-out mechanism. The IRB may decide in advance to discuss ways to opt-out of the study, or such information may be added in response to community consultation activities. FDA recognizes that in a multi-site trial, different IRBs may come to different conclusions about the feasibility of using opt-out mechanisms. Nevertheless, FDA encourages IRBs, investigators, and sponsors to work together to maximize the ability of individuals to prevent their inclusion in research to which they would object.

Community consultation activities should make the communities aware of any opt-out mechanisms that are to be used, and ensure that the community understands that efforts to inform the community may nevertheless not reach all community members. Information about available opt-out mechanisms should be part of the public disclosure materials.

For a multisite trial or a study that is reviewed using a centralized IRB process, FDA recommends that, if information about opt-out mechanisms is to be offered at any site, consideration should be given to providing the opt-out mechanism at all sites. If the IRB determines that an opt-out mechanism is feasible, emergency room (ER) staff, first responders, and emergency medical technicians (EMTs) should be trained on the opt-out mechanisms used in the study. If opt-out mechanisms are required by the study protocol, study procedures should include having ER or other staff check potential subjects for such mechanisms prior to administering the test article. Such staff should also be trained to examine, as time permits, easily accessible sources of information, such as the medical identification bracelet, for evidence that may indicate the individual's willingness or unwillingness to participate in research. See also Questions 37 and 69.

69. What is the difference between "opting-out" and providing a family member with an "opportunity to object" to a subject's participation in the study?

An "opt-out" mechanism is a way that an individual can indicate for him/herself that he/she does not want to participate in a study involving an exception from informed consent (e.g., medical jewelry, wallet card, annotation on driver's license). (See also Questions 37 and 68.)

[42] 61 Fed. Reg. 51500 (Comment #2)

An "opportunity to object" is exercised by a family member on the subject's behalf. Prior to administering the test article to the subject, if there is no legally authorized representative available, the investigator commits to attempting to locate a family member within the therapeutic window to offer the family member the "opportunity to object" to the subject's enrollment in the study.

70. How much community consultation activity is necessary?

There is no single acceptable way to accomplish or fulfill the community consultation requirements, nor will all studies require the same amount, type, or extent of community consultation activities. It is up to the IRB to review community consultation plans and assess their adequacy, in the context of local issues that may need to be considered. Different IRBs may consider more or less community consultation necessary, depending on the unique circumstances of a particular study and the community. For example, a study involving a novel treatment that is being compared with placebo may require extensive consultation with the community in which the research will be conducted and with the community from which subjects will be drawn. On the other hand, less extensive community consultation may be appropriate for a study comparing an available treatment that is considered unsatisfactory for a particular patient population or condition with another product about which much is known (e.g., an approved product that is not approved for the specific indication that is the subject of the emergency research).

71. Should sites, sponsors, or IRBs evaluate the effectiveness of community consultation and public disclosure activities?

Sites, sponsors, and IRBs are all encouraged, but not required, to explore ways and/or conduct research to evaluate the effectiveness of the community consultation and public disclosure processes.

72. Who is responsible for conducting community consultation activities? What are the respective roles of the sponsor, clinical investigator, and IRB in conducting community consultation activities?

The sponsor and clinical investigator have 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 that is reviewing the research is responsible for using the concerns expressed during the community consultation process to inform their deliberations and review.

Sponsors and clinical investigators who are conducting emergency research, and IRBs who are reviewing these studies, may not have had prior experience with community consultation. For this reason, the sponsor, and clinical investigator may find it productive to consult with one another and with the IRB to ensure that the community consultation plans are adequate and carried out in such a way that the community understands the proposed clinical investigation, including any risks and potential benefits, and has the opportunity to express any concerns.

73. How can the sponsor and clinical investigator identify the communities that should be included in community consultation activities?

To identify the communities, the sponsor and clinical investigator will need to consider the characteristics of individuals (e.g., sex, ethnicity, age, risk factors for traumatic injury) who are likely to

become the subjects in the study (i.e., the community from which subjects will be drawn). The sponsor and clinical investigator should take steps to ensure that the plans for community consultation include (but are not necessarily limited to) measures to reach members of affected groups. (See also Questions 55, 56, and 65.)

Example 1: Children with neurological impairments may be at greater risk of having seizures. Community consultation plans for a study of seizures in children should include methods to reach the community from which subjects will be drawn, in particular, the parents of such children (and, if the IRB determines that it would be appropriate, the children themselves), advocacy groups for children with neurological impairments, etc.

Example 2: Young male teenagers are at greater risk of having car accidents that may result in traumatic, life-threatening injuries. Community consultation plans for a study involving traumatic injuries should include methods to reach the community at risk, e.g., young male adolescents and their parents, teen advocacy groups, teen social groups, and high schools.

Example 3: Cardiac patients in intensive care units (ICUs) may be at higher risk for cardiac arrest. Community consultation plans for treatments for cardiac arrest could include methods to reach ICU patients, former ICU patients, family members of ICU patients, ICU physicians, nurses or other staff.

Example 4: If an external defibrillator is going to be placed in specific locations, consider whether the community from which subjects will be drawn lives in or frequents these locations, e.g., assisted living facilities for seniors, airports, etc.

74. What should the IRB do with information received during community consultation activities?

The IRB should consider the community's opinions and concerns, assess the adequacy of the consultation process, and incorporate the results of community consultation and discussion into its decision making. For this reason, the IRB may wish to directly hear 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. (See also Question 66.)

75. How can the IRB accomplish its review of community consultation plans?

Community consultation is an “additional protection” of the rights and welfare of the subjects. The IRB must find and document that this additional protection will be provided (21 CFR 50.24(a)(7)(i)). Thus, the IRB would be expected to review the plans for community consultation. Due to the complexity of these studies, such reviews may require more than one convened meeting of the IRB.

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 are 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.

  The IRB should assess whether the community consultation plans adequately provide for reaching the community from which subjects will be drawn. Because of their established interest in finding effective treatments for a particular condition, this community may provide the most meaningful feedback.

  In order to find and document that community consultation has occurred, as required in 21 CFR 50.24(a)(7)(i), the IRB should 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, in cases of limited or no input from the community(ies), the IRB may determine that additional efforts should be made to reach the community(ies).

- Consider the community concerns and incorporate the feedback, as appropriate, into its review of the protocol and informed consent document.

  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, and how to interpret the views of the various communities involved in the research, particularly if they differ, and what constitutes an appropriate response. 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 (e.g., a religious sect within a community) voice opposition to participation in the investigation. In such cases, it would be critical to determine how members of such groups can be identified. In some cases, if the community raises strenuous objections and concerns, an IRB may decide that the study should not be performed in that community.

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

76. What types of activities can sponsors and clinical investigators engage in to carry out community consultation?

The clinical investigator and sponsor (and the IRB, where appropriate) share responsibility for efforts to reach the community(ies) (21 CFR 50.24(a)(7)(i)). Sponsors and clinical investigators should provide opportunities for broad community discussion, so that representatives of the community(ies) who are likely to be interested in or may be affected by the research may discuss the proposed clinical investigation and provide specific, immediate feedback, for example, in face-to-face meetings or through an interactive website. In conducting community consultation activities, sponsors and clinical investigators should ensure that representatives from the community(ies) involved in the research have an opportunity to participate in the consultation process.

Sponsors and clinical investigators, (or the IRB, when the IRB has decided to carry out consultation activities itself) should use the most appropriate ways to provide for effective and broad-based community consultation, as appropriate, in a particular community setting. Using a variety of community consultation activities will broaden the opportunity for community involvement. Community consultation activities include (but are not limited to) the following:

- **Standing meetings**. Standing meetings, such as local civic public forums, may be better attended because such meetings are already on community members' calendars.

- **Public community meetings or other special meetings specifically organized to discuss the research.** Such meetings may be valuable in attracting participation from individuals with strong interest in the research.

- **Local radio and/or television talk shows.** Such programs allow viewers to "call in" to express their views and concerns.

- **Interactive websites, focus groups and surveys.**

Multiple methods may be needed in order to provide the information that the IRB needs from the community to review the research. Consultation activities should be widely advertised so that members of as many different groups within the community(ies) as possible are included. (See also Questions 47 and 48.)

77. How many community consultation meetings should be held?

The number of meetings held and the number of members of the community(ies) consulted should be based on a variety of factors, such as 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.

IX. 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)).

78. What is meant by "public disclosure" and what are its goals?

FDA interprets the term "public disclosure" to mean dissemination of information (i.e., one-way communication) to the community(ies), the public, and researchers about the emergency research.

The goal of public disclosure *prior to initiation of the study* is to provide sufficient information to allow a reasonable assumption that the broader community is 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 without obtaining informed consent from most study subjects.

The goal of public disclosure *after the study is completed* is to ensure that the communities, the public, and scientific researchers are aware of the study's results. Disclosure to researchers of the results, both positive and negative, of studies conducted under 21 CFR 50.24 is particularly important because such disclosure may help FDA and researchers learn from these studies involving vulnerable subjects who are unable to consent.

79. When must public disclosure occur?

Public disclosure must occur both prior to initiation of the clinical investigation (see 21 CFR 50.24(a)(7)(ii)) and after the study has been completed (see 21 CFR 50.24(a)(7)(iii)). The IRB may also determine that additional disclosure is appropriate, for example, if new information becomes available during the study. FDA recommends that all such disclosures occur promptly and that public disclosure after a study is completed or terminated occur within 1 year of the completion or termination date. (See also Questions 86 and 87 for discussion of study "completion" and "termination," respectively.)

A. PUBLIC DISCLOSURE BEFORE THE STUDY BEGINS

80. Who is responsible for public disclosure activities before the study begins?

The IRB must find and document that information about the emergency research will be publicly disclosed (21 CFR 50.24(a)(7)(ii) and (iii)).

Clinical investigators and sponsors are responsible for arranging for 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.

81. What information must be publicly disclosed?

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)). Information that should be disclosed may be found in the informed consent document, the investigator's brochure, and/or the research protocol. Similar to community consultation, appropriate disclosure includes:

- A summary of the research protocol, study design and a description of the procedures to be followed, including identification of any procedures which are experimental;
- A summary of other available treatment options and what is known about their risks and benefits;
- An estimate of how long the study will last and expected duration of the subject's participation;
- How potential study subjects will be identified;

- Information about the test article's use, including a balanced description of the risks and expected benefits and any relevant information that is known about adverse events;
- A clear statement that informed consent will not be obtained for most research subjects;
- The rationale as to why the study must be conducted using an exception from informed consent;
- A copy of the informed consent document;
- A description of the attempts that will be made to contact the LAR to obtain consent, or, if no LAR is available, a family member to provide an opportunity to object to the subject's enrollment in the study, both before and after the test article is administered (See also Questions 38-43);
- If the IRB determines that an opt-out mechanism is appropriate and feasible, a description of the way(s) in which members of the community may communicate a decision not to participate in the study (e.g., use of medical identification bracelets or wallet cards, annotation on driver's license) (See also Questions 37 and 68);
- The sites or institutions that will be participating in the research;
- Community perceptions/concerns with the study, product, and/or standard of care that were raised during community consultation and any associated modifications that were made to the research; and
- Identification of individuals to contact for more information about the study.

(See also Question 59 for the contents of appropriate community consultation.)

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.

Note that the information to be disclosed about 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 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)).

82. How should public disclosure be carried out?

FDA recommends that multiple forums and media resources be used to widely disseminate information about the study, and where additional information may be obtained. Registering the study on the National Library of Medicine's clinical trials web listing, http://www.clinicaltrials.gov, is required for "applicable clinical trials".[43] (See Question 19.) Sponsors may also consider including a reference to 21 CFR 50.24 in the registration so that it is clear to FDA that the investigation involves an exception from informed consent.

[43] P.L. 110-85, The Food and Drug Administration Amendments Act of 2007, Title VIII, Clinical Trial Databases (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110).

Other disclosure activities that may be conducted include:

- targeted mailings to households in the communities, with information about how to obtain further details;
- advertisements and articles in the English language, and if appropriate, foreign language, newspapers (Public outreach documents should be translated into languages that are common in the area served by the facility where the investigation is being conducted and in the communities from which subjects will be drawn.);
- clearly marked links and information on the sponsor's and participating hospitals' Internet web sites;
- summary materials that are accessible to non-English speaking or homeless populations who reside in the community from which research subjects are likely to be drawn;
- 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.

83. What does the IRB do with the information that has been publicly disclosed?

Ordinarily, the clinical investigator would provide the information that has been publicly disclosed (e.g., copies of newspaper advertisements, tapes or transcripts of radio and television shows, minutes of community meetings) to the IRB so that the IRB is aware that disclosure has occurred. As required by 21 CFR 56.109(g), the IRB must promptly provide the sponsor with a copy of the disclosed information. The sponsor, in turn, provides copies to FDA (21 CFR 312.54(a) and 812.47(a)). See Question 84. There may also be situations in which flow of information could vary, for example, if 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.

84. What does the sponsor do, upon receiving from the IRB the information that has been publicly disclosed?

Upon receiving copies of the information that has been publicly disclosed from the IRB, the sponsor must submit the information to FDA, i.e., to the IND/IDE and to FDA's Dockets Management at the following address:

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

See 21 CFR 56.109(g), 21 CFR 312.54(a) and 21 CFR 812.47(a).

Members of the public wishing to examine public disclosure information submitted to the docket may visit the FDA's Dockets Management Branch in person, view the materials on-line (http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-1995-S-0036), or request a copy 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

B. PUBLIC DISCLOSURE AFTER THE STUDY IS COMPLETED OR TERMINATED

85. What must be disclosed following completion of the clinical investigation?

Following completion of the clinical investigation, the IRB must find and document that sufficient information, including the demographic characteristics of the research population and the study results, will be disclosed to the community(ies) and to other researchers (21 CFR 50.24(a)(7)(iii)).[44] FDA recommends that the sponsor provide the information to the IRB(s) for review prior to disclosure.

The information disclosed should provide sufficient detail to allow a clear understanding of the study design and its results, both positive and negative, including:

- information about the primary outcome(s) of the study;
- the number and nature of adverse events associated with the test article;
- whether the study was terminated, and the basis for that decision.

Note that 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 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)).

[44] For more information about reporting results at clinicaltrials.gov, see http://chestjournal.chestpubs.org/content/136/1/295.full?sid=5bf6541b-d31a-4bc2-9460-35a4a3172186.

86. What is meant by "completion" of the clinical investigation?

Completion of the clinical investigation means the date that all study subjects have been enrolled and follow-up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol. For studies that involve more than one study site, the sponsor may consider completion of the study to occur when data from all of the study sites have been submitted to the sponsor.

87. What is meant by "termination" of the clinical investigation?

Termination of the clinical investigation refers to a situation in which a study ends or is discontinued before its planned completion (e.g., if a data monitoring committee determines that a study ethically requires termination following interim analysis of study data).[45]

88. Does FDA expect sponsors to publicly disclose information about studies that have been terminated/discontinued?

Yes. FDA expects sponsors to publicly disclose information about studies conducted under 21 CFR 50.24 that have been terminated or discontinued in the same way that sponsors must disclose information about studies that have been completed. Note that sponsors must report to FDA when a study is terminated or discontinued (21 CFR 312.31(a)(2), 812.150(b)(7)), and it is FDA's expectation that the public also be informed of terminations/discontinuances.

The agency has previously stated that there must be a scientific need to conduct clinical investigations involving subjects who are unable to consent; if previous investigations have already provided a scientific answer to a particular question, this information should be shared broadly with the research community. In the interests of limiting the number of studies that involve subjects who are not able to provide informed consent, it is FDA's position that "…broadly sharing both positive and negative results of research with the scientific community may reduce or eliminate unnecessary duplication of research that has been conducted and verified by others."[46]

89. Who is responsible for disclosing information about the study after it is completed or terminated?

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 and/or reported.

90. When should the sponsor disclose the results of the study?

Disclosure of the study results to the community(ies) should occur within a reasonable period of time following completion or termination of the investigation. For a multi-site investigation, this disclosure may require waiting until the data from all sites have been analyzed by the sponsor. FDA recommends that such disclosures occur within 1 year after the date the study was completed or terminated. (See also

[45] 21 CFR 812.3(q): "Termination means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion."
[46] 61 Fed. Reg. 51516-51517 (Comments 75-77)

Questions 86 and 87 for a discussion of study "completion" and "termination," respectively.)

91. Would reporting results of the investigation in the ClinicalTrials.gov database be sufficient for purposes of meeting the public disclosure requirements under 21 CFR 50.24 "after the study is completed"?

No. Such reporting, similar to publication of results in a scientific or medical journal, would likely satisfy the requirement to "apprise…researchers about the study, including demographic characteristics of the research population and its results." However, the information must also be disclosed to the community from which subjects are drawn and the community in which the research takes place (i.e., lay persons, members of the general public). The IRB should review plans to disclose information "following completion of the clinical investigation," to assure that the plans address appropriate ways of disclosing the results to both the lay and research communities (21 CFR 50.24(a)(7)(iii)).

92. How should the information be disclosed to the community in which the clinical investigation was conducted and the community from which the subjects were drawn (21 CFR 50.24(a)(7)(iii))?

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. It is up to the IRB to determine whether the methods described in the public disclosure plans are appropriate for the intended audience.

93. How can information about the results of the study be disclosed to other researchers?

Sufficient information may be contained in a scientific publication of the results of the completed or terminated investigation or in submissions to ClinicalTrials.gov; it may also be communicated by other means (e.g., symposia, abstracts, posting on websites).

94. Must information that is disclosed after the study is completed or terminated be submitted to FDA's Public Docket?

Yes. See 21 CFR 56.109(g), 312.54, and 812.47(a). (See also Question 84 for more information about submission of information that has been disclosed.)

X. CONTACT OF LEGALLY AUTHORIZED REPRESENTATIVES OR FAMILY MEMBERS

Contact with a subject's legally authorized representative or family member may occur at various points during the study (e.g., prior to administration of the test article, after administration of the test article, after a subject dies). This section discusses the procedures that must be developed for contacting a subject's legally authorized representative or family member at each of these points.

A. PRIOR TO ADMINISTRATION OF THE TEST ARTICLE

For each subject unable to provide informed consent, the clinical investigator participating in emergency research must commit to attempting to seek written informed consent within the therapeutic window, if feasible, from the subject's legally authorized representative (LAR; 21 CFR 50.24(a)(5)). If no LAR is available, the clinical investigator must commit 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, if feasible (21 CFR 50.24(a)(7)(v)).

95. What procedures for contacting a subject's legally authorized representative (LAR) or family member prior to administration of the test article are required by 21 CFR 50.24?

IRBs must find and document that procedures are in place for contacting and providing information to a subject's LAR 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 such procedures and information will likely parallel those approved by the IRB for use in obtaining informed consent from subjects or their LARs. IRBs must review, approve, and document that procedures are in place to be used (1) in attempting to obtain informed consent from a LAR, and (2) if no LAR is available, in attempting to contact a family member and provide an opportunity for the family member to object, as soon as is feasible, ideally, prior to enrolling a subject in the study and administering the test article (21 CFR 50.24(a)(6); see also section "IV. Therapeutic Window").

96. How can IRBs ensure that investigators make every attempt to contact the subject's legally authorized representative (LAR) or family member within the therapeutic window?

The IRB must review the procedures that will be used to attempt to contact the subject's LAR or family member within the therapeutic window, if feasible (21 CFR 50.24(a)(6)). In addition, the investigator is required to summarize efforts made to contact LARs and family members, and make this information available to the IRB at the time of continuing review (21 CFR 50.24(a)(5) and (7)(v)).

In order to summarize efforts to contact LARs and family members, the investigator may develop his/her own procedures or methods to document how this requirement is carried out. Examples of possible methods, include (but are not limited to):

- The investigator/site staff may record in the case history for each subject information about efforts that were made to contact the subject's LAR or family member (e.g., date, time, name of individual to be contacted, method of contact [phone, in person], success or failure of the effort to contact the LAR/family member, staff member who attempted the contact).

- The investigator may develop a checklist that reflects the required steps for contacting the LAR or family member. The checklist could be completed for each subject who is enrolled in the study, and included in the subject's case history or retained elsewhere in the study records.

- The investigator may appoint an individual to serve as the liaison with the LARs and families of study subjects for all research projects. The goal of having a liaison would be to assure

communication with subjects, their LARs, and their families, and thereby better protect the subjects' rights. The liaison could document efforts made to contact subjects' LARs or family members, e.g., keep a log of such contacts.

The IRB should determine how information summarizing efforts to contact LARs and family members are to be provided to the IRB (e.g., oral presentation at IRB meeting, written report by the investigator). The IRB should review the summaries provided by the investigator at the time of continuing review and, if necessary, require modification of the procedures as a condition for continuing approval of the research (21 CFR 56.109(a)). IRBs also have authority to observe or have a third party observe the consent process and the research (21 CFR 56.109(f)), and may exercise this authority to directly observe the clinical investigator's efforts to contact LARs or family members while the research is going on.

97. These studies involve an exception from informed consent requirements. Why must an informed consent document be prepared?

Although most, and perhaps all subjects will not be able to give consent, an IRB-approved informed consent document, consistent with 21 CFR 50.25, must be prepared (21 CFR 50.24(a)(6)). Informed consent is to be obtained from subjects or their legally authorized representatives when feasible. 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.

98. What is the purpose of contacting the subject's family member?

The purpose of contacting the subject's family member is to provide an opportunity for a family member to object to the subject's participation in the research (21 CFR 50.24(a)(6)). The informed consent document may be used as the source of the information that is explained to the family member; FDA recommends that a copy of the informed consent document be given to contacted family member(s).

99. If a legally authorized representative (LAR) is available, what must the investigator do?

If a LAR is available, the investigator must obtain informed consent from the LAR within the therapeutic window, if feasible, before enrolling the subject in the study (21 CFR 50.24(a)(5)). If the LAR refuses to sign the consent form, the subject must not be enrolled in the study (21 CFR 50.20).

100. If the LAR is not available, but a family member is, what must the investigator or first responder do?

The investigator or first responder must ask the family member if the family member objects to the subject's participation before enrolling the subject in the study (21 CFR 50.24(a)(7)(v)). If the family member objects or indicates that the subject would not have wanted to participate in a research study, the subject must not be enrolled in the study (21 CFR 50.24(a)(6) and (7)(v)).

101. If the subject's legally authorized representative (LAR) is available, and the LAR agrees to allow the subject to participate in the study, must the clinical investigator also contact the subject's family member?

No. When a LAR is available, the LAR can provide legally effective consent for the subject.

102. Must a family member's objection to the subject's participation in the study be in writing?

No. 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 case history or medical chart. 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 before the subject may be enrolled in the research.[47]

B. AFTER ADMINISTRATION OF THE TEST ARTICLE

103. How should a subject's family be told about the subject's participation in the study?

Clinical investigators may use various methods to ensure that each subject's family is promptly informed about the subject's participation in the study. FDA recommends that the information be communicated through personal contact with the subject's LAR or family if at all possible, and as soon as feasible after the enrollment has taken place. However, FDA recognizes that personal contact is not always possible. To ensure that the information is provided in a timely manner, the information about the study should be included in any communications with each subject's family. When face to face contact is not possible, to ensure that the subject's family receives the information, families should be notified via methods that allow receipt verification or confirmation (e.g., registered letter, e-mail with "read receipts"). The investigator could also appoint a liaison, who is responsible for contacting the subject's LAR and/or family member. Sites may consider development and use of a checklist to show the steps taken to notify a subject's family about the subject's participation in the investigation.

FDA recommends that sites not simply refer subjects and family members to websites, as these may not describe the study sufficiently nor would they allow the family members to obtain prompt, direct answers to their questions.

104. If a subject is enrolled in a study under 21 CFR 50.24, what information must be provided to the subject, the subject's legally authorized representative (LAR) or family member?

IRBs must ensure there are procedures in place to provide information at the earliest feasible opportunity about the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, to (1) the subject, if the subject's condition permits this, (2) the subject's LAR (if the subject remains incapacitated), or (3) if no LAR is available, the subject's family member (21 CFR 50.24(b)). The information must include notice that the subject, the subject's LAR (if the subject remains incapacitated), or family member (if no LAR is available) may discontinue the subject's participation in the study at any time without penalty or loss of benefits to which the subject is otherwise entitled (21 CFR 50.24(b)).

105. What is meant by "feasible"?

[47] 61 Fed. Reg. 51506 (Comment #25)

FDA interprets the term "feasible" to incorporate the idea of "practicability" and recognizes that in some instances, for example, it may not be possible to provide information to the subject (e.g., if the individual does not survive or is mentally incompetent), or to the subject's legally authorized representative or family member (e.g., if the identity of the subject is never determined).[48]

106. If a subject regains consciousness, or his legally authorized representative (LAR) is found, must consent be obtained from the subject or the subject's LAR in order to continue participation in the study?

No, consent is not required for continued participation in the study. 21 CFR 50.24(b) requires the IRB to ensure that there are procedures in place to provide information about the emergency research study to the subject, the subject's LAR or family member at the earliest feasible opportunity. However, the subject, the subject's LAR, or family member may discontinue the subject's participation at any time.

FDA regulations do not require that written informed consent be obtained from the subject or the subject's LAR once the subject is enrolled, in order to continue the subject's participation in the study. The IRB may nevertheless decide that developing an informed consent form to be used for continuation in the study would be appropriate. FDA notes, however, 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 from subject to subject, depending upon when it becomes feasible to provide the information to the subject or the subject's LAR. As FDA noted in the preamble to the Final Rule:

> 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, which 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.[49]

(See also Question 105, "What is meant by "feasible"?)

107. In the event of a subject's death, must information about the subject's enrollment in the study be provided to the subject's legally authorized representative (LAR) or family member?

Yes. IRBs must ensure that there are procedures in place to provide information about the study to the LAR or family member in the event of the subject's death, if feasible (21 CFR 50.24(b)). Although the regulations do not specify when this information should be provided, FDA recommends that the LAR or family member be told about the subject's enrollment at the earliest feasible opportunity. Informing the LAR or family member should strike a balance between prompt notice and consideration for the LAR's or family member's emotional state. It may therefore be helpful to consult with a hospital chaplain or social worker to determine an appropriate place and time, as soon as possible under the circumstances, to provide this information.

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[48] 61 Fed. Reg. 51519 (Comment #91)
[49] 61 Fed. Reg. 51519 (Comment #94)

108. When must information about the subject's enrollment in the study be provided to the subject's legally authorized representative (LAR) or family member?

The regulations require this information to be provided at the earliest feasible opportunity; see 21 CFR 50.24(b). In order to assure that the subject's LAR or family member is informed about the subject's enrollment in the study, FDA recommends that the investigator inform the LAR and family member in person if possible, or if that is not possible, the investigator may do so in writing, using a method to confirm delivery, about the subject's participation in the study.

(See also Question 105, "What is meant by "feasible"?)

109. What records must the clinical investigator maintain with respect to efforts to contact the legally authorized representative (LAR) or a subject's family member?

Clinical investigators must summarize efforts made within the therapeutic window to contact each subject's LAR for consent, or in the event that a LAR is unavailable, the subject's family member 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.

110. What access do clinical investigators have to the medical records of research subjects?

Many emergency research studies include both mortality and morbidity endpoints. Having information about both types of endpoints is very important for evaluation of the test article. Obtaining information about morbidity endpoints would generally require examination of the subject or review of the subject's medical records.

FDA's regulations require clinical investigators to prepare and maintain adequate and accurate case histories (21 CFR 312.62(b) and 812.140(a)). In general, the investigator should arrange to have access to all of the records that are generated and maintained from enrollment until discharge or death, unless the subject or the subject's legally authorized representative (LAR) or family member discontinues the subject's participation in a study. (If the subject's participation in the study has been discontinued, see also Question 111.)

If the investigator is also the subject's personal physician, then the investigator would continue to have access to the subject's medical records, unless the subject or the subject's LAR discontinues the subject's participation in the study. (See also Question 111.)

If the subject has been discharged or transferred to another medical facility (e.g., rehabilitation center, nursing home) and the investigator is no longer involved in the subject's daily care, then the investigator would have to contact the subject or his LAR to obtain the release of medical records from the subject's treating physician and/or the medical facility to the investigator.

111. If a subject, legally authorized representative (LAR), or family member discontinues the subject's participation in the study, to what records would the researcher still have access?

If a subject or the subject's LAR discontinues the subject's participation in the study, the investigator would continue to have access to data that have already been collected.

However, the investigator would not have access to the subject's medical records after the date of discontinuation (even if the subject has not been discharged from the hospital), unless the subject or the subject's LAR specifically consents to such access.

If the subject or subject's LAR has discontinued the subject's participation in the study and the subject subsequently dies, access to the individual's medical records from the point of discontinuation until the subject's death would have to be obtained from the individual's LAR. Provisions of the Health Information Portability and Accountability Act (HIPAA)[50] may apply to the release of medical records of individuals who are deceased; there may also be applicable state or local laws. See also Question 113.

(See also FDA's guidance, "Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials."[51])

112. Why is access to subjects' data (e.g., medical and study records) important? Can a subject withdraw use of his or her data that have already been collected, or results in the research database?[51]

A subject may not withdraw use of his or her data that have already been collected. FDA regulations require investigators to prepare and maintain adequate case histories recording all observations and other data pertinent to the investigation on each individual treated with the investigational product. If a subject were to be able to dictate whether already collected data are included or excluded, the potential for bias would be immense, particularly if the clinical investigation were not blinded.

FDA needs to hear about all important effects of the investigational product, so that the agency can (1) ensure that the results of the investigation are not biased, and (2) make a determination as to the product's safety and effectiveness.

113. Can information about a subject's death be collected even if the subject has discontinued participation in the study?

Yes. Although a subject may have discontinued participation in a study, data about a subject's death is contained in public vital statistics records. Access to public records is not subject to restriction under 21 CFR 50.24 or other FDA regulations.

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[50] More information about HIPAA can be obtained from the Office for Civil Rights: http://www.hhs.gov/ocr/privacy/.
[51] www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf

114. Do FDA's regulations require that informed consent be obtained from a deceased subject's family members before public records can be accessed?

No. Access to public records is not subject to restriction under 21 CFR 50.24 or other FDA regulations. The information included in death records may be accessed and collected without triggering FDA's informed consent requirements.

Under FDA's regulations, "human subject" means "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient." (See 21 CFR 50.3(g); similar language is found at 21 CFR 312.3 and 812.3(p).) FDA has interpreted its regulations as applicable only to research involving living human subjects. Since the individuals referenced are deceased, such review does not meet FDA's definition of research involving human subjects. FDA has also concluded that a limited look at public death records would, in any event, be encompassed by the exception from informed consent for emergency research.[52]

Public access to autopsy records would be determined by applicable State or local laws and regulations.

115. For emergency research under 21 CFR 50.24, involving an exception from informed consent, may an IRB or Privacy Board waive the authorization requirement that would otherwise apply under 45 CFR 164.508 of the HIPAA Privacy Rule?

Yes. Under the Privacy Rule issued to implement the Health Insurance Portability and Accountability Act of 1996 (HIPAA), an individual must generally sign a permission, known as an Authorization, before a covered entity may use or disclose the individual's protected health information (PHI) for research purposes, unless the covered entity receives documentation that an IRB or Privacy Board has waived or altered the Authorization requirement. 45 CFR 164.512(i). In the context of emergency research involving an exception from informed consent under 21 CFR 50.24, there may well be considerations present, such as the inability of the subjects to provide Authorization as a result of their medical condition, that could support an IRB or Privacy Board decision to waive the HIPAA Privacy Rule's Authorization requirement.

The Privacy Rule at 45 CFR 164.512(i) contains criteria for waiver or alteration of the Authorization requirement by an IRB or Privacy Board. In particular, the documentation of waiver approval obtained by the covered entity must, among other things, include a statement that the IRB or Privacy Board has determined that the alteration or waiver, in whole or in part, of Authorization satisfies the following criteria:

> - The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of (1) an adequate plan to protect PHI identifiers from improper use and disclosure; (2) an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law; and (3) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule.

[52] See Preamble to the October 2, 1996 Final Rule, Comment #94, 61 Fed. Reg. 51519.

- The research could not practicably be conducted without the requested waiver or alteration.

- The research could not practicably be conducted without access to and use of the PHI.

Thus, to the extent an IRB or Privacy Board has determined that the circumstances of the emergency research subject to an exception from informed consent under 21 CFR 50.24 satisfy the HIPAA Privacy Rule's waiver criteria, and has documented the waiver approval in accordance with 45 CFR 164.512(i)(2), a covered entity may use or disclose PHI for the research based on such documentation.

XI. 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)).

FDA interprets this regulatory provision to permit a sponsor to either establish an independent DMC or to secure the services of an already established DMC to exercise oversight of the clinical investigation. FDA is making this clarification to provide flexibility to sponsors in meeting the regulatory requirements.

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.[53] The DMC guidance represents FDA's current thinking on DMCs and their operations.

XII. 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/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

B. FDA's WEBSITES

Good Clinical Practice:
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
Center for Biologics Evaluation and Research (CBER):
http://www.fda.gov/BiologicsBloodVaccines/default.htm
Center for Drug Evaluation and Research (CDER):
http://www.fda.gov/Drugs/default.htm
Center for Devices and Radiological Health (CDRH): http://www.fda.gov/MedicalDevices/default.htm

[53] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

21 CFR 50.24 **APPENDIX A**

The text of 21 CFR 50.24 appears below:

Subpart B--Informed Consent of Human Subjects Sec. 50.24, Exception from informed consent requirements for emergency research.

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

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

(2) Obtaining informed consent is not feasible because:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DEFINITIONS **APPENDIX B**

Clinical investigation. (Note: The terms research, clinical research, biomedical 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 (including biological drugs): 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 or communities 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 FDA's Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006.[54]

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(m)). 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

[54] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

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 (LAR). An individual or judicial or other body authorized under applicable State or local 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. For purposes of this guidance, 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 without obtaining informed consent for most or even all subjects. 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.

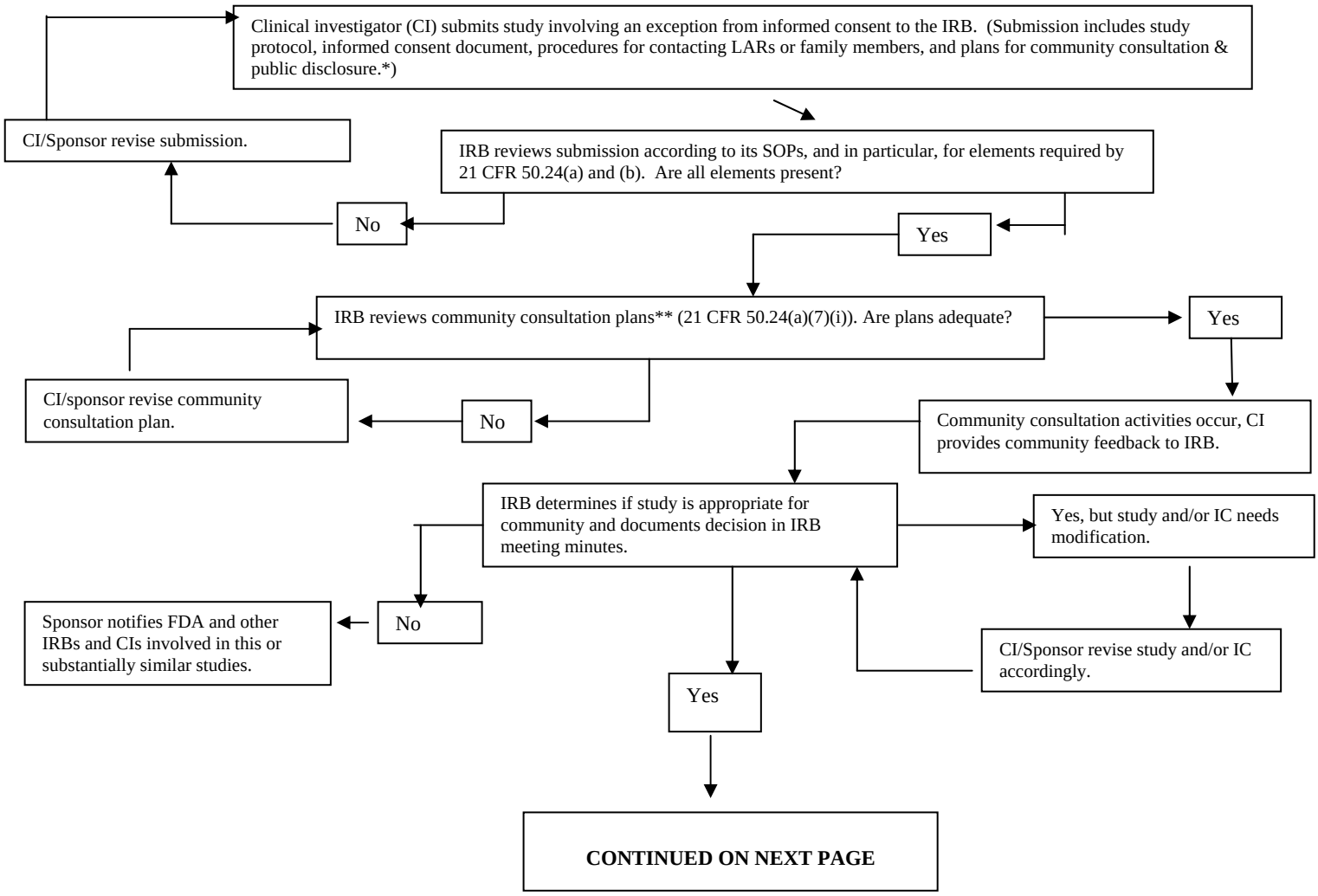
Sponsor-Investigator. An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational test article is administered or dispensed (21 CFR 312.3(b), 812.3(o)). A sponsor-investigator assumes the responsibilities of both sponsors and clinical investigators.

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.

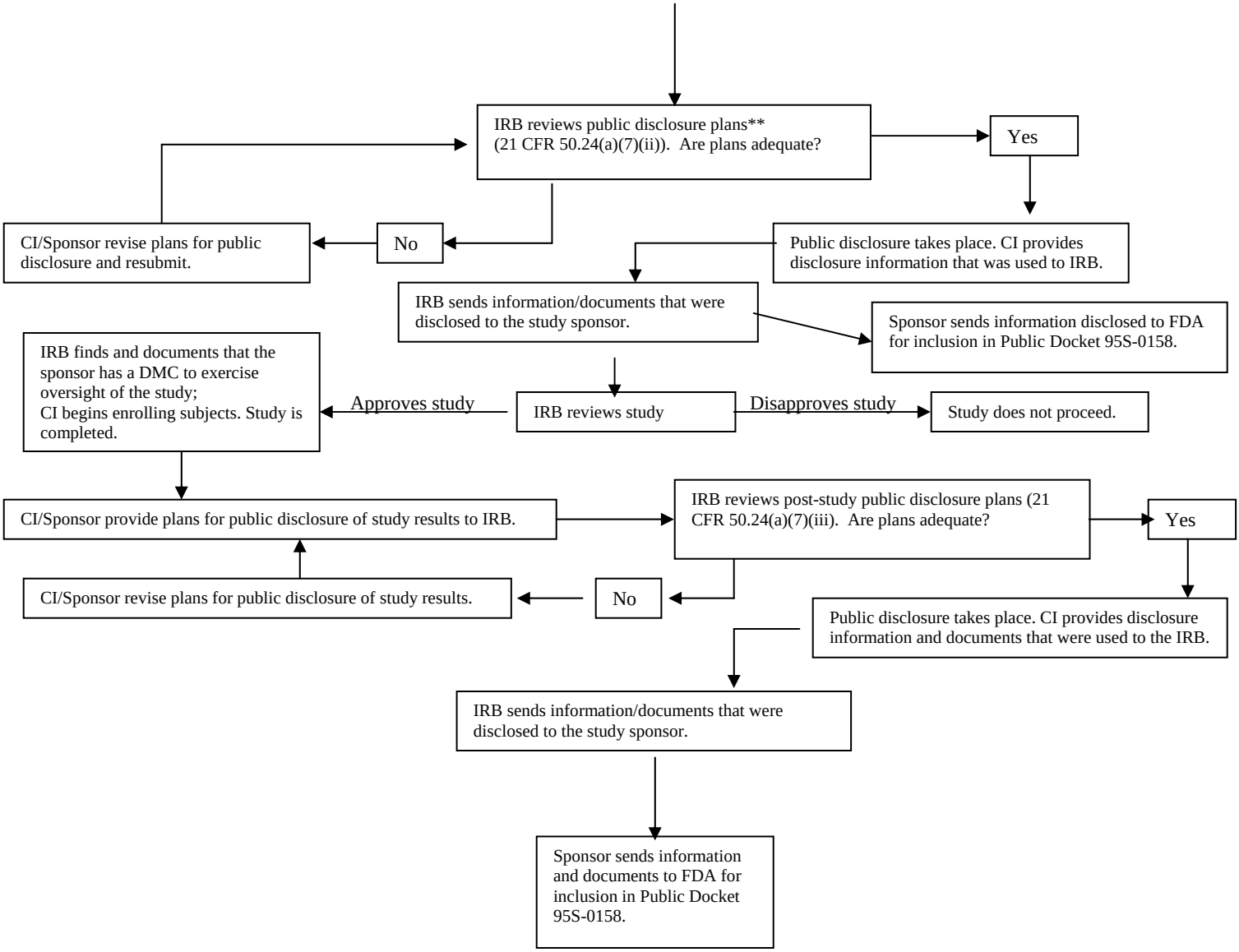
APPENDIX C

SUGGESTED FLOW CHART FOR 50.24 STUDIES

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



*The investigation 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

SUGGESTED FLOW CHART FOR 50.24 STUDIES
(Continued from Previous Page)

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