



EMERGENCY USE

05/30/2008

A. Emergency Exemption for an Investigational Drug or Biologic

1. Definitions

Emergency use of an investigational drug or biologic (emergency exemption) is defined as the use of an investigational drug or biological product for a human subject "in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain" DUHS IRB approval (21 CFR 56.102(d)). The emergency use provision of the FDA regulations (21 CFR 56.104(c)) is an exemption from prior review and approval by the IRB. The exemption may not be used unless all of the conditions previously mentioned exist.

To ensure that the emergency use will occur in compliance with FDA regulations and guidance, the investigator must establish and document that:

- (1) The patient is in a life-threatening situation.
- (2) No standard acceptable treatment is available.
- (3) There is not sufficient time to obtain a review and approval of the proposed use by a convened IRB.
- (4) The emergency use will be reported to the IRB within five working days.
- (5) Any subsequent use of the investigational product at the organization will have prospective IRB review and approval.
- (6) The use does not involve a systematic investigation designed to develop or contribute to generalizable knowledge.
- (7) Consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with and to the extent required by 21 CFR 50 and will be appropriately documented, in accordance with and to the extent required by 21 CFR 50.27 OR the situation meets the 21 CFR 50.23 exception to the requirement for consent.

Life-threatening, for these purposes (21 CFR 56.102(d)), includes the scope of both life-threatening and severely debilitating, as defined below:

Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analyses is survival. The criteria for life-threatening do not require a condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation

requiring intervention before review of an IRB protocol at a convened meeting of the IRB is feasible.

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

2. Investigator's Communication with the IRB

The IRB is required to review the emergency use of an investigational drug or biologic in a life-threatening situation in order to assess investigator compliance with FDA regulations and guidance.

Either before, or within five (5) business days after, the emergency use, the investigator must provide the IRB with a written report of the use. The report must include the items described below in "A.6. Investigator's Report to the IRB And Its Review". Investigators are advised to contact the IRB Office at the earliest feasible opportunity to document that an emergency exists and the seven required conditions (listed above) exist. An IRB Chair or Vice Chair may be contacted 24 hours a day/7 days a week by calling the main IRB telephone number (919-668-5111), and then paging the Chair/Vice Chair on call.

The IRB will assist the physician in ensuring that appropriate recipient protections are contemplated, as in A.4 below, and will remind the physician of the reporting requirements in A.6. below. The IRB Chair or Vice-Chair will review the information provided by the investigator to determine if the plans of the investigator would follow FDA regulations and guidance. In the event that the plan does not comply with FDA regulations and guidance, the Chair/Vice-Chair will provide information to the investigator for how to comply with these regulations and guidance.

The IRB will not approve a request for an emergency use unless it does so at a convened meeting. Short of this, the IRB will acknowledge that such a use will occur/has occurred, and if true, that the emergency use will be/was in compliance with FDA regulations and guidance. See "A.6. Investigator's Report To The IRB And Its Review" below.

3. Informed Consent – The Process

Even for such an emergency use, the process of informed consent must meet FDA requirements found at 21 CFR 50.25. The investigator is required to obtain legally effective informed consent of the subject or the subject's legally authorized representative, using an appropriate consent document.

4. Informed Consent – The Document

The investigator is required to obtain informed consent of the subject or the subject's legally authorized representative, using an appropriate consent

document, except as described above in A.3. The consent document must contain the following elements:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (9) A statement that FDA may inspect the records associated with this research.

When appropriate, the following elements of information shall also be provided to each subject in this emergency setting:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- (3) Any additional costs to the subject that may result from participation in the research.
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- (6) The approximate number of subjects involved in the study.

In order for the signed consent form to be suitable for inclusion in the Duke Hospital medical record, the document must be printed on the Duke M0 345 form.

The investigator may adapt a consent form from a previously approved research study involving the use of the investigational drug or biologic to be suitable for this emergency use by removing all references to that research study but retaining all references to the research use of the investigational drug or biologic. Or the investigator may develop a new consent form that includes all of the above elements of informed consent. An IRB Specialist, Medical Writer or a Chair/Vice-Chair may assist the investigator in this process.

5. Waiver of Informed Consent

The investigator is expected to obtain the written consent of the subject or the subject's legally authorized representative for this emergency use. However, if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23(a)), then the investigational use may proceed without the consent of the subject or the subject's legally authorized representative.

- (1) The subject is confronted by a life-threatening situation necessitating the use of the drug or biologic.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legally authorized representative.
- (4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the investigational drug or biologic is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above have been met, the investigator should make the determination and, within five (5) business days after the use of the drug or biologic, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within five (5) business days after the use of the drug or biologic (21 CFR 50.23(c)) See A.6. Investigator's Report to the IRB And Its Review below.

The report is received in the IRB Office, and an IRB Specialist reviews it for completeness, and then forwards it to an IRB Chair or Vice-Chair for review to ensure that the emergency use was in compliance with FDA regulations and

guidance. Then a convened IRB is notified of this report. The report is filed by the IRB Specialist in the Emergency Use folder.

6. Investigator's Report To The IRB and Its Review

Investigators are required to submit to the IRB Office a notification of anticipated emergency use of an investigational drug or biologic prior to its use, or a report on the emergency use of the investigational drug or biologic within five (5) business days following its use. The notification or report must contain the following information:

- a. A description of the emergency and the use of the investigational drug or biologic.
- b. Documentation that the seven required conditions (see A.1. above) were met.
- c. A statement from the investigator that no new use of the investigational drug or biologic will occur without prior IRB review and approval.
- d. A copy of the unsigned informed consent document used for the research, when applicable.
- e. When the emergency use occurred without prior consent of the subject or the subject's legally authorized representative, a copy of the letter from the independent physician that the four required conditions were met (see A.5 above).

Once the report is received in the IRB Office, an IRB Specialist will check the Emergency Use folder to determine if this investigational drug or biologic has been used before under the Emergency Use provision. That information, plus the report, is reviewed by an IRB Chair/Vice Chair to ensure that the emergency use will follow/followed FDA regulations and guidance. In the event that the use does not comply with FDA regulations and guidance, the Chair/Vice-Chair will include this information in the report of the emergency use to the convened IRB.

At the next available meeting the convened IRB will be notified of the emergency use and the Chair/Vice-Chair's findings. If the investigator's actions are found by the Chair/Vice-Chair to have not been in compliance with FDA regulations and guidance, the investigator will be evaluated for serious or continuing noncompliance as required by DUHS IRB policy.

The investigator is informed by the Chair/Vice-Chair in writing that if the investigator anticipates the need to use the investigational drug or biologic in additional subjects, prospective review by the IRB is required. The investigator's report and the IRB's response will be filed by the IRB Specialist in the Emergency Use folder.

If the IRB finds that the investigator has not complied with FDA regulations and guidance, the Institutional Official or designee will notify both the investigator, the sponsor and the FDA of the IRB's finding of investigator noncompliance. This too will be filed by the IRB Specialist in the Emergency Use folder.

Some manufacturers will agree to allow the use of the investigational drug or biologic, but their policy requires "an IRB approval letter" before the investigational drug or biologic will be shipped. If it is not possible, within the time available, for the investigator to prepare an IRB protocol and the IRB staff to convene a quorum of the IRB to review the protocol, an IRB Chair/Vice-Chair will provide for the sponsor a written statement that the IRB has acknowledged the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). This is not an "IRB approval," but the acknowledgment statement may be acceptable to the manufacturer for allowing the shipment to proceed. The IRB Specialist will add the acknowledgment statement to the other correspondence about the emergency use, and file it all in the Emergency Use folder.

This exemption allows for one emergency use of an investigational drug or biologic without prospective IRB review, provided that such an emergency use is reported to the IRB within five (5) business days. After the emergency use of an investigational drug or biologic, the investigator should evaluate the likelihood of a similar need occurring again, and if future use is likely, submit an IRB protocol requesting approval for such future use. If a second individual requires identical treatment and the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the submitted protocol, the investigator may follow the procedures described above for notification of the IRB about the proposed use.

According to FDA, a person treated under FDA's emergency use provision is considered to be a research subject (21 CFR 56.102(e)). Therefore the outcome of the emergency use, including any unanticipated problems, must be reported to FDA. (This report may be via the drug or biologic sponsor. If the investigator is also the sponsor, the sponsor-investigator will comply with the procedures described in "Responsibilities of an Investigator Who Is Also a Sponsor".) However, OHRP views the person differently (OHRP Guidance (May 15, 1991). OHRP agrees that emergency medical care for patients may be provided without regard to IRB review and approval. Whenever emergency care is initiated without prior IRB review and approval, OHRP holds that the patient may not be considered to be a research subject, and such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity sponsored or funded by a DUHS agency.

Note that the conduct of planned research in life-threatening emergency situations where obtaining prospective informed consent has been waived, as provided by 21 CFR 50.24, differs from this emergency use provision. That research plan must be approved in advance by the FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Community consultation must also be sought. That type of research is described in more detail below in Section C.

B. Emergency Use of an Unapproved Device

The emergency use of an unapproved device is permissible if the FDA requirements for emergency use are met.

1. Definitions

Emergency use of an unapproved device is defined as the use, with a human subject in a life-threatening situation, of an unapproved device for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval (FDA approval for marketing). An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an investigational device exemption (IDE). However, emergencies may arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE.

Each of the following conditions must exist to justify the emergency use, and therefore the investigator must establish and document that:

- (1) The patient is in a life-threatening condition that needs immediate treatment.
- (2) No generally accepted alternative for treating the patient is available that provides an equal or greater likelihood of saving the patient's life.
- (3) Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.
- (4) There is not sufficient time to obtain a review and approval of the proposed use by a convened IRB.
- (5) The emergency use will be reported to the IRB within five working days.
- (6) Any subsequent use of the investigational product at the organization will have prospective IRB review and approval.
- (7) The use does not involve a systematic investigation designed to develop or contribute to generalizable knowledge.
- (8) Consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with and to the extent required by 21 CFR 50 and will be appropriately documented, in accordance with and to the extent required by 21 CFR 50.27 OR the situation meets the 21 CFR 50.23 exception to the requirement for consent.

Life-threatening, for these purposes (21 CFR 56.102(d)), includes the scope of both life-threatening and severely debilitating, as defined below:

Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analyses is survival. The criteria for life-threatening do not require a condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review of an IRB protocol at a convened meeting of the IRB is feasible.

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

In the event that a device is to be used in circumstances meeting the criteria described above, IRB would expect the investigator to follow as many subject protection procedures as possible. These include:

- (1) Obtaining an independent assessment by an uninvolved physician.
- (2) Obtaining informed consent from the patient or the patient's legally authorized representative.
- (3) Notifying the IRB.
- (4) Obtaining authorization from the IDE holder, if an approved IDE for the device exist.

2. Investigator's Communication with the IRB

The IRB is required to review the emergency use of an investigational device in a life-threatening situation in order to assess investigator compliance with FDA regulations and guidance.

Either before, or within five (5) business days after, the emergency use, the investigator must provide the IRB with a written report of the use. The report must include the items described below in "B.6. Investigator's Report To The IRB And Its Review". Investigators are advised to contact the IRB Office at the earliest feasible opportunity to document that an emergency exists and the eight required conditions (listed above in B.1.) exist. An IRB Chair or Vice Chair may be contacted 24 hours a day/7 days a week by calling the main IRB telephone number (919-668-5111), and then paging the Chair/Vice Chair on call.

The IRB will assist the physician in ensuring that appropriate recipient protections are contemplated, as in B.4 below, and will remind the physician of the reporting requirements in B.6. below. The IRB Chair or Vice-Chair will review the information provided by the investigator to determine if the plans of the investigator would follow FDA regulations and guidance. In the event that the plan does not comply with FDA regulations and guidance, the Chair/Vice-Chair

will provide information to the investigator for how to comply with these regulations and guidance.

The IRB will not approve a request for an emergency use unless it does so at a convened meeting. Short of this, the IRB will acknowledge that such a use will occur/has occurred, and if true, that the emergency use will be/was in compliance with FDA regulations and guidance. See “B.6. Investigator’s Report To The IRB and Its Review” below.

3. Informed Consent – The Process

Even for such an emergency use, the process of informed consent must meet FDA requirements found at 21 CFR 50.25. The investigator is required to obtain legally effective informed consent of the subject or the subject’s legally authorized representative, using an appropriate consent document.

4. Informed Consent – The Document

The investigator is required to obtain informed consent of the subject or the subject’s legally authorized representative, using an appropriate consent document, except as described above in B.3. The consent document must contain the following elements:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(9) A statement that FDA may inspect the records associated with this research.

When appropriate, the following elements of information shall also be provided to each subject in this emergency setting:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- (3) Any additional costs to the subject that may result from participation in the research.
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- (6) The approximate number of subjects involved in the study.

In order for the signed consent form to be suitable for inclusion in the Duke Hospital medical record, the document must be printed on the Duke M0 345 form.

The investigator may adapt a consent form from a previously approved research study involving the use of the investigational device to be suitable for this emergency use by removing all references to that research study but retaining all references to the research use of the investigational device. Or the investigator may develop a new consent form that includes all of the above elements of informed consent. An IRB Specialist, Medical Writer or a Chair/Vice-Chair may assist the investigator in this process.

5. Waiver of Informed Consent

The investigator is expected to obtain the written consent of the subject or the subject's legally authorized representative for this emergency use. However, if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23(a)), then the investigational use may proceed without the consent of the subject or the subject's legally authorized representative.

- (1) The subject is confronted by life-threatening situation necessitating the use of the investigational device.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

- (3) Time is not sufficient to obtain consent from the subject's legally authorized representative.
- (4) No alternative method of approval or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the investigational device is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the investigator should make the determination and, within five (5) business days after the use of the investigational device, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within five (5) business days after the use of the investigational device (21 CFR 50.23(c)). See B.6. Investigator's Report To The IRB and Its Review below.

The report is received in the IRB Office, and an IRB Specialist reviews it for completeness, and then forwards it to an IRB Chair or Vice-Chair for review to ensure that the emergency use was in compliance with FDA regulations and guidance. Then a convened IRB is notified of this report. The report is filed by the IRB Specialist in the Emergency Use Folder.

6. Investigator's Report to the IRB, and Its Review

Investigators are required to submit to the IRB Office a notification of anticipated emergency use of an investigational device prior to its use, or a report on the emergency use of the investigational device within five (5) business days following its use, whether or not the IRB was notified prospectively of the planned use. The notification or report must contain the following information:

- a. A description of the emergency and the use of the investigational device.
- b. Documentation that the eight required conditions (see B.1. above) were met.
- c. A statement from the investigator that no new use of the investigational device will occur without prior IRB review and approval.
- d. A copy of the unsigned informed consent document used for the research, when applicable.
- e. When the emergency use occurred without prior consent of the subject or the subject's legally authorized representative, a copy of the letter from the independent physician that the four required conditions were met (See B.5 above).

Once the report is received in the IRB Office, an IRB Specialist will check the Emergency Use folder to determine if this investigational device has been used before under the Emergency Use provision. That information, plus the report, is reviewed by an IRB Chair/Vice Chair to ensure that the emergency use will follow/followed FDA regulations and guidance. In the event that the use does not

comply with FDA regulations and guidance, the Chair/Vice-Chair will include this information in the report of the emergency use to the convened IRB.

At the next available meeting the convened IRB will be notified of the emergency use and the Chair/Vice-Chair's findings. If the investigator's actions are found by the Chair/Vice-Chair to have not been in compliance with FDA regulations and guidance, the investigator will be evaluated for serious or continuing noncompliance as required by DUHS IRB policy.

The investigator is informed by the Chair/Vice-Chair in writing that if the investigator anticipates the need to use the investigational device in additional subjects, prospective review by the IRB is required. The investigator's report and the IRB's response will be filed by the IRB Specialist in the Emergency Use folder.

If the IRB finds that the investigator has not complied with FDA regulations and guidance, the Institutional Official or his designee will notify both the investigator, the sponsor and the FDA of the IRB's finding of investigator noncompliance. This too will be filed by the IRB Specialist in the Emergency Use folder.

Note that a physician may not conclude an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE procedures may require more time than is available. Physicians should be aware that the IRB expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

After an unapproved device is used in an emergency, the investigator should:

- (1) Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use.
- (2) If an IDE for the use does exist, notify the sponsor of the emergency use, or
- (3) If an IDE does not exist, notify FDA of the emergency use and provide the FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the investigator or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with the FDA and the FDA disapproves the IDE application, the device may not be used even if circumstances constituting an emergency exist. Developers of devices that could be used in emergencies are expected to anticipate the likelihood of emergency use and obtain an approved IDE for such uses.

Some manufacturers will agree to allow the use of the investigational device, but their policy requires "an IRB approval letter" before the investigational device will be shipped. If it is not possible, within the time available, for the investigator to prepare an IRB protocol and the IRB staff to convene a quorum of the IRB to review the protocol, an IRB Chair/Vice-Chair will provide for the sponsor a written statement that the IRB has acknowledged the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). This is not an "IRB approval," but the acknowledgment statement may be acceptable to the manufacturer for allowing the shipment to proceed. The IRB Specialist will add the acknowledgment statement to the other correspondence about the emergency use, and file it all in the Emergency Use folder.

According to FDA, a person treated under FDA's emergency use provision is considered to be a research subject (21 CFR 56.102(e)). Therefore the outcome of the emergency use, including any unanticipated problems, must be reported to FDA. (This report may be via the device sponsor. If the investigator is also the sponsor, the sponsor-investigator will comply with the procedures described in "Responsibilities of an Investigator Who Is Also a Sponsor".) However, OHRP views the person differently (OHRP Guidance (May 15, 1991). OHRP agrees that emergency medical care for patients may be provided without regard to IRB review and approval. Whenever emergency care is initiated without prior IRB review and approval, OHRP holds that the patient may not be considered to be a research subject, and such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity sponsored or funded by a DUHS agency.

Note that the conduct of planned research in life-threatening emergency situations where obtaining prospective informed consent has been waived, as provided by 21 CFR 50.24, differs from this emergency use provision. That research plan must be approved in advance by the FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Community consultation must also be sought. That type of research is described in more detail below.

C. Exception From Informed Consent For Studies Conducted In Emergency Settings

1. Background

The federal regulations for the protection of human subjects in research require informed consent, with a few narrow exceptions. The FDA regulation (21 CFR 50.24) and OHRP policy (OPRR Report 97-01) provide a narrow exception to the requirement for obtaining informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The exception applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but

who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized representative present to represent them. The regulation allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies.

2. Vulnerable population

Persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. The lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of such research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by the IRB.

While the FDA regulation (21 CFR 50.24) is silent on the inclusion of prisoners, pregnant women and fetuses, or children in such planned emergency research, OHRP policy (OPRR Report 97-01) specifically includes children but excludes prisoners or pregnant women and fetuses.

3. Concurrence of a licensed physician

The FDA regulation specifically requires the concurrence of a licensed physician "who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation" (21 CFR 50.24(a)). This requirement is similar to 21 CFR 50.23 which requires an independent assessment by a physician not otherwise participating in the research when an investigational product is to be used in a life-threatening situation. Because 21 CFR 50.24 permits an exception from the requirement for informed consent for a group of subjects, the case-by-case independent determination is replaced by the general concurrence of a licensed physician. Because the documented concurrence of the physician is required for approval of these studies, the IRB will ensure that meeting minutes specifically reflect this affirmative vote. For research not subject to FDA regulation but subject to OHRP policy, such concurrence of a licensed physician is not required.

4. Life threatening situation

The regulation requires that subjects must be in a life-threatening situation requiring intervention before consent from a legally authorized representative is feasible. *Life-threatening* includes diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted (21 CFR 312.81). People with such conditions as long-term or permanent coma, stroke, and head injury may survive for long periods, but the likelihood of survival is not known during the therapeutic window of treatment. People with these conditions are clearly at increased risk of death due to, for example, infection, pulmonary embolism, or progression of disease. The regulation applies in such situations if the intervention, in order to be successful, must be given before consent is

feasible. The informed consent waiver provision is not intended to apply to persons who are not in an emergent situation, such as individuals who have been in a coma for a long period of time and for whom the research intervention should await the availability of a legally authorized representative of the subject.

Subjects need not be comatose, but the medical condition under study must prevent obtaining valid informed consent. The IRB must determine, based on the specific details of the individual clinical investigation (including the window of opportunity for treatment), the procedures the investigator must follow to attempt to obtain informed consent before enrolling a subject in an investigation without such consent. The IRB is knowledgeable about DUHS procedures regarding the use of advance medical directives and must assess whether the proposed clinical investigation is consistent with those procedures.

5. IRB responsibilities for research subject to FDA regulations

In addition to the IRB responsibilities found at 21 CFR 56.111, the IRB must make the following determinations. A convened board will do so, the determinations will be recorded in the meeting minutes, and the investigator will be notified of the review outcome as described elsewhere in these policies and procedures.

a. Informed consent

The IRB must determine, based on the specific details of the individual clinical investigation (including the window of opportunity for treatment), the procedures the investigator must follow to attempt to obtain informed consent before enrolling a subject in an investigation without such consent.

If the IRB determines that it is not appropriate to waive the requirement for informed consent because there is a reasonable way to identify prospectively the individuals likely to become eligible for the study, then the exception under 21 CFR 50.24 would not apply. In that case, only a subject with the condition (or his or her legally authorized representative) who gave prior consent may be enrolled in the study. Those individuals who either did not make a decision or who refused participation would be excluded from participation in the study. While an exception to the requirement for obtaining informed consent from each human subject, or his or her legally authorized representative, would not be allowed under 21 CFR 50.24, the individual exception allowed under 21 CFR 50.23 (see Sections A and B above) might be applicable in some circumstances as determined by the IRB.

If scientifically sound research can be practicably carried out using only consenting subjects (directly, or with the involvement of the subject's legally authorized representative), then the research must be carried out without involving non-consenting subjects. The term *practicably*, as used here, means, for example, (1) that recruitment of consenting subjects does not bias the science, and the science is no less rigorous as a result of restricting it to

consenting subjects; or (2) that the research is not unduly delayed by restricting it to consenting subjects.

Appropriate efforts must be made by the investigator to obtain consent from subjects prior to enrollment. These procedures must be documented in the protocol and/or by the IRB, and the efforts made by investigators must be documented in the material presented to the IRB for its continuing review.

b. Role of family members

Unlike other regulations concerning the provision of consent or permission for research participation, 21 CFR 50.24 specifically includes family members as decision makers because the opportunity for an available family member to object to a potential subject's participation in such a clinical investigation provides an additional and an important protection to these subjects. Otherwise, if consent from a subject or the subject's legally authorized representative were not feasible, the eligible individual could be enrolled into the investigation. Thus, by permitting a family member (even one who is not a legally authorized representative) to object to an individual's inclusion in the investigation, a further protection is provided to that individual.

A family member is defined by both FDA (21 CFR 50.3(m)) and OHRP (OPRR Report 97-01) as 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.

A family member must be provided an opportunity to object to the potential subject's participation, if feasible within the therapeutic window, when obtaining informed consent from the subject is not feasible and a legally authorized representative is not available. This does not constitute legally effective informed consent if the family member is not a legally authorized representative under North Carolina law. (See DUHS HRPP policy on Use of Legally Authorized Representative for the order of authority in North Carolina to provide consent on behalf of another adult for participation in clinical research presenting the prospect of therapeutic benefit to the subject.) Under 21 CFR 50.24, only one family member would need to be consulted and agree or object to the patient's participation in the research. If family members were to disagree, the researcher and family members would need to work out the disagreement. But the investigator is advised not to proceed with involving the patient as a research subject if intra-family disagreement cannot be resolved.

c. Consent of participating subjects

The IRB must determine whether it is possible or desirable, given the nature of the clinical investigation, to have an actual document that is a meaningful informed consent document for continued participation in the research that could be signed by the subject or legally authorized representative. Such a document

that would be signed after entry into an investigation would not constitute consent for what had already occurred; it could, however, serve to document that the subject consented to continued participation in the investigation. If this document is determined to be appropriate, it must include information that the subject, legally authorized representative, or family member was informed of the subject's inclusion in the clinical investigation, the details of the investigation, and other information contained in the informed consent document. This document must be retained for at least 6 years after the completion of the clinical investigation.

d. Community consultation

The community from which eligible subjects will be drawn must be informed of the planned research. In addition, broad consultation with the community is needed for this type of research. The IRB must provide an opportunity for the community from which research subjects may be drawn to understand the proposed clinical investigation and its risks and benefits and to discuss the investigation. The IRB must consider this community discussion in reviewing the investigation. Based on this community consultation, the IRB may decide, among other things, that it is appropriate to attempt to exclude certain groups from participation in the investigation, or that wider community consultation and discussion is needed. The IRB could consider, for example, having public meetings in the community to discuss the protocol; meetings with local civic groups; inviting public comment through print and broadcast media including local talk radio shows; establishing a separate panel of members of the community from which the subjects will be drawn; including consultants to the IRB from the community from which the subjects will be drawn; enhancing the membership of the IRB by adding members who are not affiliated with the institution and are representative of the community; or developing other mechanisms to ensure community involvement and input into the IRB's decision-making process. The IRB recognizes that multiple methods may be needed in order to provide the supplemental information it will need from the community to review this research.

The IRB must determine what information to disclose to the community. This information could include, but may not necessarily be limited to, the information that is found in the informed consent document, the investigator's brochure, and the research protocol. The IRB must consider how best to publicly disclose, prior to commencement of the clinical investigation, sufficient information to describe the investigation's risks and benefits, such as relevant information from the investigator's brochure, the informed consent document, and the investigational protocol. Initial disclosure of information will occur during the community consultation process. Disclosure of this information to the community will inform individuals within the community about the clinical investigation and permit them to raise concerns and objections.

e. Notice to the North Carolina Medical Care Commission

When the IRB reviewing the research study has authorized the start of the community consultation process, but before the beginning of that process, notice of the proposed research study shall be provided to the North Carolina Medical Care Commission, in keeping with 10A NCAC 13B .3302, Minimum Provisions of Patient's Bill of Rights. The notice shall include at a minimum:

- (1) the title of the research study;
- (2) a description of the research study, including a description of the population to be enrolled;
- (3) a description of the planned community consultation process, including currently proposed meeting dates and times;
- (4) an explanation of the way that people choosing not to participate in the research study may opt out; and
- (5) the contact information for the IRB and the principal investigator.

The Medical Care Commission may publish all or part of the above information in the North Carolina Register, and may require the institution proposing to conduct the research study to attend a public meeting of the Commission to present and discuss the study or the community consultation process proposed.

f. Report to the community

(i) The scientific community:

A comprehensive summary of data from the completed trial must be provided to the research community in order to permit other researchers to assess the results of the clinical investigation. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, a publication may need to be supplemented by additional information. Information to be disclosed must include the demographic characteristics (age, gender, and race) of the research population. For a multi-center investigation, the sponsor and/or lead investigators will be responsible for analyzing the results of the overall investigation, including the demographic characteristics of the research population, and these results must be published or reported in the lay press within a reasonable period of time following completion of the investigation.

(ii) The broader lay community

Both before and after publication of the scientific report, the IRB will be responsible for determining appropriate mechanisms for providing information about the outcome of the research to the community from which research subjects were drawn. The IRB could consider any of the methods successfully used to solicit community consultation and comment early in the review process, for example, the print and broadcast media, including local talk radio shows, and having public meetings in the community to discuss the study results. The IRB recognizes that multiple methods may be useful in order to reach members of the broader lay community.

g. New IND or IDE

For research subject to FDA regulation, 21 CFR 50.24 requires the submission of a separate IND or IDE to ensure that FDA reviews the application before the study may proceed. The IRB must receive a copy of the FDA approval letter to the sponsor that indicates the IND or IDE number related to this study approved under this regulation.

h. IRB disapproval

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under 21 CFR 50.24 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 is obligated to promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor. Other clinical investigation would be "substantially equivalent" if it proposes to invoke this exception from informed consent and involves basically the same medical conditions and investigational treatments. For research not subject to FDA regulation but subject to OHRP policy, such documentation to OHRP is not required.

i. Review of protocol changes

If there is a change in the protocol, there must be re-review of the protocol by the IRB. If the change is minor, it may be eligible for expedited review under 21 CFR 56.110 and 45 CFR 46.110, which permit the IRB to use an expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. If the change is significant (such as, if it adversely affects risk), it must be reviewed by a convened board.

j. Periodic continuing review

The IRB must stipulate during the study's initial review the frequency of continuing review. This will likely be less than one year, but in no case will it be more than one year.

The IRB will regard the study as active until all research-related activities have ended, specifically including the process of community notification of study results and conclusions.

6. Research not subject to FDA regulations

This research is subject both to the specific DHHS (OHRP) provisions noted above in sections C.2., C.3., C.5.b., C.5.e., and C.5.h. and to the following requirements.

The IRB responsible for the review, approval, and continuing review of the research must find and document that the research is not subject to FDA regulations at 21 CFR 50, must approve both the research and a waiver of informed consent, and must:

- a. find and document that the research *is not subject* to FDA regulations at 21 CFR 50.24, and
- b. find and document and report to the Office of Human Research Protections (OHRP) that the following conditions have been met relative to the research:
 - (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 involved in the research 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 research.
 - (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 research 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 research could not practicably be carried out without the waiver.
 - (5) The proposed research protocol 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 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 in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. 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 research consistent with paragraph (b)(7)(v) of this waiver.

(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 research will be conducted and from which the subjects will be drawn;
- (ii) public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;
- (iii) public disclosure of sufficient information following completion of the research 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 research; 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 research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, 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 research, the details of the research 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 research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a

subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; 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.

7. Actions required of the investigator

The investigator proposing to conduct research under this provision must do so in full compliance with federal regulations and guidance, IRB policies and procedures and additional IRB directives specifically related to this research. Such directives may relate to:

- a. Disclosure of information about the proposed study to the community of eligible participants in a manner prescribed by the IRB.
- b. The conduct of community consultation in a manner prescribed by the IRB.
- c. Attempting to obtain informed consent before enrolling a subject in the investigation without such consent.
- d. Obtaining, after study initiation, subject consent if the subject becomes capable of giving legally effective informed consent.
- e. Disclosing information about the completed study to the community of eligible participants in a manner prescribed by the IRB.
- f. Reporting the research findings to the scientific community

The investigator will be notified of these special directives in writing by the IRB Chair/Vice-Chair following the convened meeting where the directive was approved. The investigator must notify the IRB of each directive's implementation and its outcome either in response to a specific request by the IRB or at the time of periodic continuing review of the study.