Emergency Use of a Test Article

Contrary to common usage, the terms **"emergency use" and "compassionate use" are not synonymous**. Become aware of the specific, separate standards for emergency use and compassionate use/expanded use to avoid violating federal regulations and Woman's IRB policy regarding the use of unapproved drugs, biologics and devices. For information about Compassionate Use, refer to the Compassionate Use policy.

Definitions

Compassionate Use: The compassionate use provision provides a path to accessing investigational devices that have not received FDA approval or clearance for patients for whom the treating physician believes the device may provide a benefit in diagnosing, monitoring, or treating their disease or condition. Refer to the policy, Compassionate Use.

Emergency use: the use of an investigational drug or biological product with 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 IRB approval [21 CFR 56.102(d)].

Expanded Access: a potential pathway for patients with a serious or life-threatening disease or condition to access an investigational medical device that has not been approved or cleared by the FDA for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available through one of three mechanisms:

- Emergency Use
- Compassionate Use (or Individual Patient/Small Group Access)
- Treatment Investigational Device Exemption (IDE)

Life-threatening: 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 end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely debilitating: 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.

Test article: any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act

Treatment Investigational Device Exemption (IDE) - An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the

study. During the course of the clinical trial, if the data suggest that the device is effective, then the trial may be expanded under a new IDE to include additional patients with life-threatening or serious diseases. This is called a treatment IDE. A licensed physician who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56. The sponsor of a treatment IDE must submit progress reports on a semi-annual basis to all reviewing IRB's and the FDA until the filing of a marketing application.

When Can a Test Article be Used in an Emergency Situation?

- You wish to use a test article on a human
- The patient is in a life-threatening situation
- A severely-debilitating condition exists
- There is no standard acceptable treatment available for the patient's condition
- There is not time to obtain IRB approval

Steps for Using an Emergency Test Article

- Contact the Human Protections Administrator for information about the use of the test article with regard to requirements
- Contact the IRB Chair for discussion of the emergency use criteria
- Contact the sponsor and FDA to obtain an IND or IDE for emergency use
- Obtain consent, or waive consent, for the patient receiving treatment
- Report the use of the test article to the IRB within 5 business days
- Complete follow-up reporting requirements to the sponsor and FDA after use

These steps are discussed in the policy below, and an Emergency Use checklist is available.

Before a test article is used

Obtaining an Emergency IND:

The emergency use of an unapproved investigational drug or biologic requires an IND. The FDA has provisions for obtaining emergency Investigational New Drug applications. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

Current Federal law requires that a drug be the subject of an approved marketing application before it can be distributed across state lines. In order for a sponsor to ship investigational drugs to investigators across state lines, it must seek an exemption from that legal requirement. The

IND is the means through which the sponsor technically obtains this exemption from the FDA. Under FDA regulations, emergency use of a test article, other than a medical device, is a clinical investigation. The patient is considered a participant and the FDA may require data to be reported in a marketing application.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.310(d)].

FDA Contacts for Obtaining an Emergency IND

1. Drug Products: Division of Drug Information | (888) 463-6332 | (301) 796-3400
2. Biological Blood Products: Office of Blood Research and Review | (HFM-300) | (301) 827-3518
3. Biological Vaccine Products: Office of Vaccines Research | (HFM-400) | (301) 827-3070
4. On Nights and Weekends: Office of Crisis Management & Emergency Operations Center | (866) 300-4374 | (301) 796-8240

Emergency Use of Devices

Emergency use of an unapproved device may occur before an Investigational Device Exemption application is approved.

Expanded access to an investigational device under the emergency use mechanism is intended to provide patients and physicians with access to investigational devices to address immediately life-threatening situations when there is no available alternative and no time to use existing procedures to obtain FDA approval. Emergency use may apply if the device is being studied in clinical trials under an investigational device exemption (IDE) such as when a physician who is not part of the IDE clinical study wishes to use the device to treat a patient in an immediately life-threatening situation. An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. Emergency use may also apply if there is no IDE or ongoing clinical studies for the device.

Criteria for emergency use:

- The patient has a life-threatening condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

If all of the above criteria are met, an unapproved device may be used in an emergency situation without prior approval by the FDA.

For the use of an investigational device, the physician should follow as many patient protection measures as possible. This includes obtaining:

1. Informed consent from the patient or a legal representative (see Informed Consent requirements below);
2. Clearance from the institution as specified by institutional policies;
3. Concurrence of the IRB chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the IDE sponsor, if an approved IDE exists for the device

Type of Expanded Access	Brief Definition	FDA approval required?	Follow-up Reports to the FDA
Emergency use	Use of an investigational device when an **individual patient is in a life-threatening situation and needs immediate treatment** (there are no alternative options and no time to use existing procedures to get FDA approval for the use)	No	Yes
Compassionate use	Use of an investigational device to **treat or diagnose an individual patient or a small group of patients** with a serious disease or condition when there are no available alternative options	Yes	Yes
Treatment Investigational Device Exemption	Use of an investigational device to **treat or diagnose a group of patients** with a serious or immediately life-threatening disease or condition when the device is also being studied for the same use under an approved Investigational Device Exemption.	Yes	Yes

Emergency use of a device must be reported to FDA. If there is an IDE for the device, the IDE sponsor must notify the FDA of the emergency use within 5 days through submission of an IDE Report (§812.35(a)(2)). This follow-up report should include a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.

If no IDE exists, the physician should submit to the FDA a follow-up report within 5 days on the use of the device including: a description of device used, details of the case, and the patient protection measures that were followed. The report should be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

Conducting One-Time Emergency Use of a Test Article

Review of *prospective* emergency use research protocols is not provided by Woman's Hospital IRB at this time.

Clinical emergency use of a test article may be conducted for life-threatening medical conditions for which there is no other effective or available treatment. Patients receiving a test article in an emergency use situation (as defined by FDA) may not be considered research participants. Any data collected from the emergency use intervention cannot be used as part of a prospective research protocol and data or outcome obtained from this use should not be included in any report of a research activity under HHS.

21 CFR 56.104 allows a clinical investigation to be exempt from IRB review if it involves emergency use of a test article, provided that such emergency use is reported to the IRB with five working days. This exemption from prior IRB review may be used for one-time emergency use of a test article, and only if all of the conditions in 21 CFR 56.104(d) are met:

- the situation is life-threatening or severely debilitating
- there are no alternatives or standard treatment available
- there is not sufficient time to obtain IRB approval
- the use is reported to the IRB within 5 business days
- any subsequent use is subject to IRB review

The IRB should review emergency use protocols and consent forms when subsequent use of the emergency drug or device is anticipated. The IRB will provide a copy of any information that has been publically disclosed regarding any emergency use of a drug or device. Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined.

The FDA allows for treatment of subsequent individuals if the only obstacle is that the IRB has not had sufficient time to convene to review this emergency use. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review.

Subsequent emergency use of the test article

FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. The IRB will monitor the emergency use of the test article with the investigator to ensure that continued use does not occur, which would constitute research.

FDA regulations may require data from an emergency use to be reported in a marketing application.

IRB Requirements

If time allows, the investigator should generate a letter to the IRB Chair describing the emergency use situation. The letter should document compliance with the FDA emergency use regulations, which include:

 An explanation that a life-threatening situation exists for which no standard treatment is available and
 The treatment must be implemented expeditiously and there is insufficient time to obtain IRB approval

Woman's Hospital IRB requires an independent assessment from an uninvolved physician with expertise in the area concerned. If time allows, a committee should be formed consisting of the IRB Chair, Human Protections Administrator (HPA), Medical Director of Research, and an uninvolved physician, at a minimum, to review the emergency use. If the IRB Chair is unavailable, the Vice Chair, or another member of the IRB if the Vice Chair is unavailable, may act as Chair in this capacity. The IRB Chair may elect to include other members of the IRB, if they are available. This committee may meet in person to discuss the emergency use, or by phone consultation if that proves more efficient.

The IRB Chair will generate a response letter to the investigator indicating that an emergency situation does indeed exist and there is not sufficient time to convene the IRB. The letter will state that the IRB Chair has acknowledged the use of the test article. This letter does not represent IRB review or approval; this letter only represents acknowledgement that the IRB Chair has been notified of the emergency use. The FDA regulations do not provide for expedited IRB approval in emergency situations.

The IRB should be notified of the emergency use within five working days. Under emergency use circumstances an informed consent form provided by the sponsor may be used to document consent.

Some manufacturers will agree to allow the use of the test article, but their policy requires an IRB approval letter before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB office can prepare a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not IRB approval, the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

Informed Consent under Emergency Use

Informed consent must be obtained from the subject (or subject's legally-authorized representative) prior to implementation of any emergency test article, if it is possible to be obtained. If the subject's medical condition renders him incapable of giving informed consent

and a legally authorized representative is not available, the requirement of obtaining informed consent prior to implementation of the test article may be waived.

Waiver of informed consent under emergency use

Under Section 46.101(i) the HHS Secretary issued in the Federal Register (October 31, 1996) a waiver of the 45CFR46 requirement for obtaining and documenting informed consent for research activities in which a human subject is engaged for emergency therapy. This waiver can be granted if the subject's medical condition prevents him from giving informed consent and a legally authorized representative is not available. This waiver applies to research involving children, but does *not* apply to research involving fetuses, pregnant women, and IVF.

The following conditions must be met to waive obtaining informed consent prior to implementation of emergency use of a test article and must be certified in writing by both the investigator and a physician who is not otherwise participating in the clinical investigation pursuant to 21CFR50.23(a):

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article.

(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 legal 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 test article 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 clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical use. The investigator must notify the IRB within five working days after the use of the test article [21 CFR 50.23(c)].

If informed consent cannot be obtained due to the subject being unable to provide informed consent due to the medical condition, or intervention must be administered before consent is feasible, the enrolled subject or a legally authorized representative should be informed of the use as soon as possible. Procedures should include notifying the subject or legally authorized representative that he can withdraw at any time and details of the research as contained in the informed consent form.

Responsibilities of the Investigator/Physician After the Test Article is Used

1. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)]. The notification should

1. Describe the test article that was used, including any IND or IDE numbers
2. The conditions necessitating the emergency use,
3. The status of the participant,
4. Confirmation that written consent was obtained,
5. If written consent was not obtained, provide written certification from the investigator and a physician who is not otherwise participating in the clinical investigation that:

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

2. For Investigational devices, the emergency use should be reported to the FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed and patient outcome information.
3. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. If the investigator believes the investigational product may need to be used again, a new protocol submission should be submitted to the IRB. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Helpful Guidance:

OHRP: Emergency Medical Care and Research

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-medical-care-and-research/index.html

FDA: Emergency Use of an Investigational Drug or Biologic

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-investigational-drug-or-biologic

FDA: Emergency / Expanded Access for Medical Devices

https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/expanded-access-medical-devices