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Overview and Definitions

The University and the FDA wish to support a physician's obligation to treat a seriously ill patient with all available modalities. The emergency use provision in federal regulations allows physicians restricted access to investigational treatments that would be otherwise off-limits [21 CFR 56.104(c) ^[1] and 21 CFR 56.102(d) ^[2]].

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 UCSF policy regarding the use of unapproved drugs, biologics and devices.

Different FDA regulations apply to the different types of test article use, and the terminology can be confusing. Use the following definitions:

Research use

Most administration/use of unapproved devices, drugs or biologics is part of a systematic clinical trial. All clinical investigations, including pilot studies, require prior IRB review and approval. Almost all clinical studies are conducted under an Investigational Device Exemption (IDE) ^[3] or an Investigational New Drug (IND) ^[4] exemption obtained from the FDA.

Emergency use

Use of an investigational drug, biological product, or medical device generally requires either an IND (for unapproved drugs and biologics) or an IDE (for unapproved devices).

However, the FDA's ?emergency use? exemption allows the use of a test article on a human subject in a life-threatening situation ^[5] in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

A physician who treats a patient under emergency use provisions must justify the treatment according to strict criteria, consult with the IRB, and fulfill specific follow-up/reporting responsibilities in a timely manner, as described in detail below.

Note: Emergency use is emergency clinical care and does not meet the DHHS definition of research. IRB agreement that a particular case meets FDA criteria for emergency use applies to the treatment of one patient only and is not the same as IRB approval to conduct a research study.

Compassionate use and expanded access

Expanded access ^[6], sometimes called "compassionate use," is the use outside of a clinical trial of an investigational medical product. A patient may be able to receive the product (when appropriate) through expanded access when enrollment in a clinical trial is not possible, e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials.

Such use of an investigational drug, biologic or device falls into one of the following expanded access treatment mechanisms. **Prior IRB review and approval is required**, even if only one patient is to be treated under the following mechanisms. In most circumstances, prior approval by the FDA is also required.

Expanded Access Treatment Mechanisms:

Treatment INDs or Individual Patient Access to Investigational Drugs/Devices for Serious Diseases: These mechanisms are primarily intended to give seriously ill patients access to experimental drugs or devices where no comparable or satisfactory alternative treatment is available. Although the test article sponsor is expected to continue conventional clinical trials and pursue marketing approvals with due diligence, expanded access studies involve systematic use of experimental treatments, and, with very rare exceptions, require the same review and approval as research, including both IRB approval and FDA approval in the form of an IDE (medical device) or an IND (drug/biologic).

Open Protocols (Parallel Track, Open Label Protocol, Open Label IND) or Continued Access IDEs: These uncontrolled studies are typically used when controlled trials have ended and treatment is continued so the subjects may continue to receive the benefits of the test article until marketing approval is obtained. Informed consent and prior IRB approval are required.

Enrollment exception to the inclusion/exclusion criteria of an approved protocol

To allow treatment of a single patient who does not meet the entry criteria of an IRB-approved protocol, the PI should submit a written request to IRB ^[7] for a one-time, one-patient enrollment exception. Such a request, which should be rare, must be justified in terms of serving the best interests of the patient.

See the enrollment exception info on Modification page ^[8] for info on how to submit this request. Note: IRB approval is required **before** the exception can be made.

Research in emergency medicine

Planned research designed to evaluate emergency care treatments is not emergency use. As with all other clinical research, prospective IRB review and approval are required before a clinical study in emergency medicine can begin. See the Research in Emergency Settings ^[9] page for details, including info on the emergency medical research waiver of informed consent.

Innovative treatment (off-label use)

Emergency use provisions apply to investigational drugs, biologics and devices. The innovative use of a marketed drug or device (sometimes called "off-label" use) for individual patient treatment rather than for research purposes does not require IRB review.

Important Note: Treating a series of patients in a novel or innovative manner and analyzing the results for publication is research requiring prior IRB review. Review the "Innovative Procedures, Treatment or Instructional Methods" section of the Quick Guide: Activities Requiring IRB Review ^[10] for more info.

Humanitarian Device Exemption (HDE)

An HDE is a special approval given by the FDA that allows marketing a device that is designed to treat or diagnose a condition that affects no more than 8000 individuals per year. An HDE is given even though the efficacy of the device has not been tested or proven, because it is not financially feasible to do the usual clinical testing when so few individuals are affected. The FDA requires IRB approval prior to use of a Humanitarian Use Device (HUD), even though the use is not considered research.

The IRB requires a standard application, use of a consent form similar to research consent and annual review. The initial review for this application must be done by the full committee; however, the annual continuing reviews can be done through expedited procedures. Call the IRB office for additional guidance. UCSF guidelines are under development.

Ethical Considerations of Emergency Use Provisions

Although treating a seriously ill patient under emergency use provisions is motivated by humaneness and compassion, there are several ethical issues to consider regarding the emergent use of an experimental treatment.

Unproven efficacy

Physicians are often enthusiastic about the possible benefits of an investigational drug or device. However, the lack of FDA approval usually means the safety and efficacy have not been scientifically proven. The possible, but unproven, benefits of the experimental treatment must be weighed against its risks and against the possible benefits of available alternatives.

Lack of scientific benefit

Although the FDA tracks test article emergency use, clinical data obtained from the use contributes little to the overall statistical evaluation of the treatment. The potential benefit is only to a single patient; there is little potential societal benefit from increasing scientific knowledge.

Informed consent

The physician should carefully consider that the standard is higher for emergency use informed consent than for routine clinical care. Given the life-threatening or potentially disabling condition of the patient, it is critical that the consent form clearly states that there is no guarantee of benefit from the emergency use procedure. Guidance on obtaining informed consent is provided below.

Emergency Use Criteria

The following criteria must be met to comply with federal regulations and University policy on emergency use of unapproved drugs, biologics and devices.

1. The test article is used one time per institution to treat a single patient.
2. The patient has a condition that is life-threatening or severely debilitating.
3. No standard treatment is available.
4. There is not sufficient time to obtain IRB review and approval.
5. The emergency use is reported to the IRB within five working days; when possible, the treating physician should consult with the IRB prior to use.

6. Consent will be sought and documented from the prospective participant or the participant's legally authorized representative, unless the criteria for the exception to the requirement for consent are met (see below).
7. The treatment is not part of a systematic investigation designed to develop or contribute to generalizable knowledge (that is, treatment will not be incorporated into a project that meets the DHHS definition of research requiring IRB review).

Important Note: The FDA holds the institution to high standards when justifying emergency use. Past lessons tell us that it is very difficult to argue that there's no acceptable alternative treatment and that there is "not sufficient time" to obtain prior IRB approval.

Emergency Use Requirements

If the use of an unapproved drug, device or biologic can be justified as emergency use, the physician must fulfill several time-sensitive requirements. A separate **Emergency Use Compliance Checklist** ^[11] also is available.

Contact the IRB (prior to the emergency use, when possible)

Detailed instructions are provided in the Compliance Checklist ^[11]. A brief summary follows:

- If a treating physician is planning to use an unapproved drug, biologic, or device under emergency use provisions, he/she must contact the IRB office at 415-476-1814 prior to the emergency use, if at all possible. The IRB office is well staffed and calls regarding emergency use are handled as expeditiously as possible.
- The IRB office will ask a few questions and direct the treating physician to the appropriate Chair or Vice Chair. The Chair will review the case with the physician to determine if the case meets FDA criteria for emergency use.
- If it is known in advance that it will not be possible to obtain consent from the patient or the patient's legally authorized representative, the physician should also discuss with the Chair whether the use meets FDA criteria for waiving consent.
- If the Chair agrees that the proposed treatment meets the FDA criteria for emergency use and, if applicable, waiver of consent, the IRB will send the physician a letter documenting that the FDA criteria have been met. Sponsors often require a copy of this letter from the IRB before they will ship or release the test article. Early interaction with the IRB will help expedite the preparation of the letter, if needed.

The treating physician also must submit a post-use report ^[12] to the IRB within five (5) working days of use, as described below.

Obtain informed consent

Before the emergency use, every effort should be made to obtain informed consent signed by the patient or the patient's surrogate (legally authorized representative). If written informed consent is not possible, there are special provisions for an informed consent waiver.

Whether the physician writes the consent or uses a template consent from another source (e.g. the sponsor/manufacturer of the test article), the emergency use consent should contain the elements of informed consent found in the UCSF template

[13], but need not follow the UCSF format and wording. It must be stated clearly that:

- there is no guarantee of benefit and
- the treatment is experimental and not approved by the FDA.

Because the FDA exempts emergency use from requirements for IRB review, prior IRB approval of the consent form is not needed. A signed copy of the informed consent must be included in the post-use written report [12].

Waiver of Consent:

If prior consent is not possible, federal regulations [21 CFR 50.23] allow a waiver under the following conditions:

- If at all possible, before the emergency use the treating physician and a physician not involved in clinical investigation of the test article certify in writing that:
 1. The patient is confronted with a life-threatening situation.
 2. The physician cannot communicate with the patient.
 3. Time is not sufficient to obtain consent from the patient's surrogate (legally authorized representative).
 4. No alternative method of approved or generally recognized therapy is available that provides equal or greater likelihood of saving the patient's life.
- If immediate use of the test article is needed to preserve the patient's life, and there is not sufficient time to secure an independent physician's determination that the four conditions described above apply, the treating physician must have the written determination reviewed and signed by an independent physician within five working days after the emergency use of the test article.
- Include a copy of the written determination with the post-use written report.

Notify the FDA

The FDA must be notified of the emergency use by the holder of the IND (investigational drugs and biologics) or IDE (medical devices). The FDA usually provides a new number for the specific emergency use.

- **Industry-sponsored IND/IDE:** The physician must notify the manufacturer or sponsor about the emergency use and the sponsor notifies the FDA for IND/IDE approval.
- **Physician-sponsored IND/IDE, or if no IND/IDE exists:** The physician must notify the FDA about the emergency use at the numbers provided below.

Product	Office/Division to Contact
Drug products	Division of Drug Information [14] (888) 463-6332 (301) 796-3400
Biological blood products	Office of Blood Research and Review (240) 402-8360

Biological vaccine products	Office of Vaccines Research and Review Contact the Office of Communication, Outreach and Development at: (240) 402-7800
On nights and weekends	Office of Crisis Management & Emergency Operations Center (866) 300-4374 (301) 796-8240
Devices ^[15]	Center for Devices and Radiological Health 1-800-638-2041 301-796-7100 The sponsor must notify the FDA of the emergency use within 5 days through a submission of an IDE Report ^[16] describing the details of the case and the patient protection measures that were followed.

Submit a post-use written report

For tracking purposes, the FDA requires the treating physician to document the emergency use in writing and submit the report to the IRB within five (5) working days. The report must include the treatment justification, a copy of the informed consent, and a description of the results obtained from using the test article.

The physician may use the Post-use Written Report Form ^[12] or a separate report that must contain the following information:

1. Physician's name, department address, phone numbers
2. Name of test article (unapproved drug, biologic, or device)
3. Name of sponsor (IND/IDE holder for test article)
4. Date of IRB notification
5. Date the test article was used
6. Name of patient
7. Rationale for test article use
8. Results of test article use: If not available within the initial reporting period (5 working days), results must be reported to IRB within 10 working days of the occurrence.
9. The IND or IDE number.
10. Copy of signed informed consent form or justification to waive informed consent.

IMPORTANT NOTE: Any adverse event that results from the emergency use of an investigational drug or device is subject to adverse event reporting requirements ^[17].

Consequences of Noncompliance with Federal Regulations

If the strict emergency use requirements are not met, both the physician and the institution may suffer strong sanctions.

- Physician noncompliance may result in termination or suspension from treating patients in any and all FDA-regulated studies.

- If the institution fails to provide guidance to physicians and to establish clear procedures, the institution's ability to conduct FDA-regulated research may be restricted.

IRB Oversight:

- To help physicians comply with emergency use regulations, the IRB determines whether each use complies. Most often, this is done when the physician discusses the proposed use with an IRB Chair or Vice Chair before the patient is treated. When prior consultation is not possible, a Chair will review the post-use written report. If the post-use written report indicates consent was waived, the IRB Chair or Vice Chair also will review the waiver to determine if it complies with FDA requirements.
- For both the emergency use itself and for a waiver of consent (if applicable), the IRB will issue a letter certifying compliance or informing the physician of noncompliance. In the case of noncompliance ^[18], the IRB will follow its usual procedure to determine whether the noncompliance is a serious or continuing problem requiring additional action.

Forms

- [Emergency Use Compliance Checklist](#) ^[11]
- [Emergency Post-Use Written Report Form](#) ^[12]

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Links

- [1] <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.104>
- [2] <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=56.102>
- [3] <http://irb.ucsf.edu/investigational-devices>
- [4] <http://irb.ucsf.edu/investigational-new-drugs-and-biologics>
- [5] <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm>
- [6] <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>
- [7] <http://hrpp.ucsf.edu/modification#exceptions>
- [8] <http://irb.ucsf.edu/node/201#exceptions>
- [9] <http://irb.ucsf.edu/research-emergency-settings>
- [10] <http://irb.ucsf.edu/quick-guide-activities-requiring-irb-review>
- [11] <http://hrpp.ucsf.edu/sites/hrpp.ucsf.edu/files/emergency-use-checklist.pdf>
- [12] <http://hrpp.ucsf.edu/sites/hrpp.ucsf.edu/files/emergency-use-report-form.doc>
- [13] <http://irb.ucsf.edu/consent-and-assent-form-templates>
- [14] <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082585.htm>
- [15] <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceE>
- [16] <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceE>
- [17] <http://irb.ucsf.edu/adverse-event>
- [18] <http://irb.ucsf.edu/protocol-violation-or-incident>