

CARILION CLINIC INSTITUTIONAL REVIEW BOARD

Standard Operating Guidelines

Title: 4.1: Investigational Drugs and Biologics: EMERGENCY AND TREATMENT USE OF INVESTIGATIONAL DRUG	
Original Date: March 2006	Revision Date: 1-08, 8-23
Primary Sponsor: Human Research Protections Office	Approved By: Director of the Human Research Protections Office

Objective:

To set forth guidance for the Carilion Institutional Review Board (IRB) review and approval of research involving the emergency and treatment use of investigational drugs.

General Description:

Food and Drug Administration (FDA) Human Subjects Regulations allow a test drug to be used in emergency situations without prior IRB approval as long as the emergency use is reported to the IRB within five working days. When emergency care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity.

Procedure:

Emergency

Use the Emergency Drug Treatment Form and submit to the IRB. Subsequent use of the test drug must be reviewed by the IRB. An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

Treatment

Various FDA regulations and policies also allow certain persons not enrolled in clinical trials to obtain access to investigational drugs:

- A treatment investigational new drug is a treatment protocol that is added to an existing Investigational New Drug Application (IND) that allows physicians to treat qualifying subjects according to the protocol. The IND must also provide additional data on the drug's safety and effectiveness. Treatment investigational new drugs are available for subjects with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists.
- A "single patient use" allows a physician to obtain access to an investigational drug for the treatment of a single patient. Usually, the patient is in a desperate situation and unresponsive to other therapies or is in a situation where no approved or generally recognized treatment is available. Further, there usually is little evidence that the

proposed therapy is useful but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained through the sponsor under a treatment protocol. Access may also come through the FDA by first obtaining the drug from the sponsor and then submitting a Treatment IND to the FDA requesting authorization to use the investigational drug for treatment use.

- The Parallel Track Mechanism makes available promising investigational agents as quickly as possible to persons with AIDS and other HIV-related diseases while generating data on the safety and effectiveness of the drug. Under FDA policy, persons with AIDS and HIV-related diseases who are not able to take standard therapy or for whom standard therapy is no longer effective, and who are not able to participate in ongoing controlled clinical trials would have access to promising investigational drugs. Applications for consideration of experimental therapies for Parallel Track expanded availability must be submitted to the FDA as amendments to existing INDs.

Emergency Use of an Investigational Drug or Biologic

The emergency use of test articles frequently prompts questions from IRBs and investigators. This guidance document addresses three areas of concern: emergency investigational new drug requirements, IRB procedures and informed consent requirements.

Emergency Use Investigational New Drug (IND)

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

Also see FDA Information Sheet "Emergency Use of an Investigational Drug or Biologic."

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. 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.

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]

FDA contacts for obtaining an emergency IND:

<i>For drug products contact:</i> Drug Information Branch (HFD-210) (301) 796-3400-4573 <i>For a biological blood product contact:</i>	Nights and weekends: Division of Emergency/Epidemiological Operations (HFC-160) (301) 796-8240 or (866) 300-4374
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**Office of Blood Research and
Review**
(240)-402-8360

For a vaccine product contact:
**Office of Vaccines Research
And Review**
(240) 402-7800

Emergency Exemption from Prospective IRB Approval

Emergency use is defined as 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)].

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. 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.

Life threatening, for the purposes of section 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 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 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.

Institutional procedures may require that the IRB be notified prior to such use; however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five-day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give full IRB approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

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, some IRBs have sent to the sponsor 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 an IRB approval, the acknowledgment letter has been acceptable to manufacturers and will allow the shipment to proceed.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless 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)]:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject
- Time is not sufficient to obtain consent from the subject's legal representative
- 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 investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent may be waived is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

These investigations involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury) cannot provide informed consent. The research must have the prospect of direct benefit to the patient and must involve an investigational product that, to be effective, must be administered before informed consent from the subject or the subject's legally authorized representative can be obtained and in which there is no reasonable way to identify prospectively individuals likely to become eligible for participation.

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

Also see FDA Information Sheet: "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research"

Expanded Access of Investigational Drugs

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.[21 CFR 312.310, 21 CFR 312.315, 21 CFR 312.320]

Open Label Protocol or Open Protocol IND

These are usually uncontrolled studies, carried out to obtain additional safety data (Phase III studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.

Treatment IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

Also see FDA Information sheet: "Treatment Use of Investigational Drugs"

There are four requirements that must be met before a treatment IND can be issued:

- The drug is intended to treat a serious or immediately life-threatening disease
- There is no satisfactory alternative treatment available
- The drug is already under investigation, or trials have been completed
- The trial sponsor is actively pursuing marketing approval

Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

Group C Treatment IND

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and subjects treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105]. Even though

FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document, which must be used if there has been no local IRB review.

Parallel Track

The Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.