Emergency Use of Unapproved Drugs and Biologics
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Purpose:

To establish policy with respect to the emergency use of unapproved drugs and biologics.

Definitions:

1. IRB approval means the determination of the IRB that the research has been reviewed and may be conducted within the constraints set forth by the IRB and by other institutional and federal requirements.

2. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research is not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

3. Life threatening includes the scope of both life-threatening and severely debilitating. Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; or 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 such as blindness, loss of hearing, loss of arm, leg, hand or foot, paralysis or stroke.

5. Test article/Investigational article (or product) means 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.
Policy:

1. Conditions for Emergency Use

Food and Drug Administration (FDA) regulations and this policy pertain to the “emergency use”, without prospective IRB review and approval of an unapproved drug or biological product in a patient with a life-threatening problem under the following conditions:

- the condition is life threatening necessitating use of the test article
- no standard acceptable treatment is available
- there is not sufficient time to obtain prospective IRB approval.

If IRB review is possible, prospective IRB approval must be sought. Only if treatment of a life-threatening condition is necessary before IRB approval is made, does this “emergency use” policy apply.

2. Emergency Use of Test Articles Contrasted with Research on Emergency Use of Test Articles

Federal regulations stipulate that research activities may not be started, even in emergency situations, without prior IRB review and approval. Please note the following requirements whenever “emergency use” of an investigational product is initiated without prior IRB approval:

- the patient may not be considered a research subject;
- the emergency treatment may not be claimed as research; AND data obtained from this treatment may not be included in any report of a research activity or used for research purposes.

Note – FDA acknowledges that it would be inappropriate to deny emergency use of an investigational drug or biologic considered necessary for the treatment of a second individual if the use was unexpected and the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. Subsequent emergency use of the unapproved article may not occur unless the physician or another person obtains approval of an Investigational New Drug/Investigational Device Exemption (IND/IDE). If the application for subsequent is disapproved by the FDA, the article may not be used even if the circumstances constituting an emergency exist. Manufacturers or developers of investigational articles that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an IND/IDE for such uses.
Federal regulations, guidance documents and this policy are not intended to limit the authority of a physician to provide emergency medical care to the extent permitted under applicable federal, state or local law. Rather, this policy pertains only to the use of an investigational or test article in emergency situations.

The emergency use of an unapproved investigational drug or biologic requires an IND unless the intended subject meets the inclusion criteria of an existing study protocol, or an approved study protocol exists. The IND requirement may be met if the manufacturer makes the drug or biologic available for the emergency use under the company’s IND.

If the emergency situation does not allow time for submission of an IND or amendment of the manufacturer’s IND, only the FDA may authorize shipment of the test article in advance of the IND submission (or amendment). Requests for such authorization may be made by telephone or other rapid communication means to the FDA.

3. **NSU IRB Requirements for Emergency Use of Test Articles**

FDA regulations and NSU IRB policy permit an exception to the requirement for prior IRB review and approval for purposes of “emergency use” if all the following conditions are met:

- It is the use of a test article;
- A human subject has a life-threatening situation;
- No standard acceptable treatment is available; AND
- There is not sufficient time to obtain IRB approval

This exemption is allowed only for a **one-time institutional use** of a test article without prospective IRB review. Any subsequent use of the investigational product must have prospective IRB review and approval. If there is uncertainty as to whether emergency use of a particular investigational drug or device has occurred at NSU, or at another facility by an NSU student or staff member, relevant information should be sought from the NSU IRB office prior to the “emergency use.”

If possible prior to an “emergency use”, the physician seeking to provide the life-saving treatment should notify the NSU IRB of this intent by any available means.
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This notification must be in writing and include:

- A description of the circumstances that warrant the administration of a test article without IRB approval.
- A statement that the subject is confronted with a life-threatening situation that requires immediate medical intervention before the IRB can be convened.
- Confirmation that no alternative method of approved or generally recognized therapy is available to provide an equal or greater likelihood of saving the subject's life.
- A description of how the test article will be used.
- A copy of the informed consent document to be used; or
- A statement that the informed consent document cannot be obtained because of difficulty in communication with the subject and/or insufficient time to contact the subject's legal representative.

Both the primary physician and a physician who is not participating in the clinical administration of the test article must sign this document.

The IRB office shall forward the physician's notification to the IRB chair or designee who will review the circumstances of the “emergency use” to verify whether it meets the conditions of the federal regulation and he/she, or the IRB office, shall so notify the physician in writing either by postal mail, electronic mail, or interoffice mail of the results of that review. This notification should not be construed as IRB approval. Rather, the IRB office shall use this prior report to initiate tracking to ensure that the investigator files a report within the five day time-frame required by federal regulation and this policy. A copy of this report shall also be provided to the signatory official (VP for Institutional Effectiveness) and the director of clinical operations.

Physicians authorizing the “emergency use” of the test article should follow as many subject protection procedures as possible including:

- Obtaining an independent assessment by an uninvolved physician
- Obtaining authorization from the IND/IDE holder (as appropriate)
- Notifying institutional officials as specified by clinical/institutional policies
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- Obtaining informed consent from the patient or a legal representative
- Notifying the IRB Office

Within five (5) working days following the emergency use of a test article, the physician must notify the IRB in writing of the emergency use of a test article pursuant to FDA regulations at 21 CFR 56.104(c). This report should include an explanation of the use, how and when the use took place, and justification based on FDA criteria for “emergency use” including why prospective IRB review was not possible, the informed consent process, and, if applicable, how IND/IDE requirements were met. This report should include a copy of the properly executed (signed) informed consent document or a statement that informed consent document could not be obtained because of difficulty in communication with the patient and/or insufficient time to contact the patient’s legal representative. The report should also include follow-up information on the condition of the patient in the days after the test article has been administered. The report is to be submitted in writing and must include a copy of the consent form that was (or is about to be) signed by the subject or the subject’s authorized representative.

If further uses of a test article are anticipated, a study application must be submitted for review and approval by the convened IRB in addition to the submission of the 5-day report. Subsequent use of the test article is contingent upon this IRB approval and an FDA-approved IND/IDE.

There are two options available to applications for further uses of a test article.

- Not collecting data for research: If the test article use does not include collecting data for research purposes, a treatment IND/IDE should be obtained from the FDA and a corresponding study application should be submitted for IRB approval. IRB approval is required for the use of a treatment IND even if the use does not involve research.

- Collecting data for research: if research data is collected pursuant to the use of the test article, a research IND/IDE should be obtained from the FDA and a corresponding study application should be submitted for IRB approval.

FDA regulations do not permit expedited IRB approval in emergency situations and terms such as “interim,” “compassionate,” or “temporary,” may not be used to authorize an expedited approval process. IRB approval of an emergency use requires review by the convened IRB or, if the conditions outlined above are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without an IRB approval (providing all requirements are met).
4. 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:

- 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 5 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)].

5. Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been 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. Such studies are usually not eligible for the emergency approvals described above. 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.

6. 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 (IND) used for these purposes reflect the recognition by the Food and Drug Administration (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.

OPEN LABEL PROTOCOL OR OPEN PROTOCOL IND

These are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 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 Institutional Review Board (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.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) 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 patients 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.

EMERGENCY USE 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].

Drug Study Designs

Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. A well-controlled study permits a comparison of subjects treated with the new agent with a suitable control population, so that the effect of the new agent can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy, or observer expectations. FDA regulations [21 CFR 314.126] cite five different kinds of controls that can be useful in particular circumstances:
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- placebo concurrent control
- dose-comparison concurrent control
- no-treatment concurrent control
- active-treatment concurrent control, and
- historical control

No general preference is expressed for any one type, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that, because it is relatively difficult to be sure that historical control groups are comparable to the treated subjects with respect to variables that could effect outcome, use of historical control studies has been reserved for special circumstances, notably cases where the disease treated has high and predictable mortality (a large difference from this usual course would be easy to detect) and those in which the effect is self-evident (e.g., a general anesthetic).

Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

There are three principal difficulties in interpreting active-control trials. First, active-control trials are often too small to show that a clinically meaningful difference between the two treatments, if present, could have been detected with reasonable assurance; i.e., the trials have a high "beta-error." In part, this can be overcome by increasing sample size, but two other problems remain even if studies are large. One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have
powerful stimuli toward assuring study excellence. Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise. The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful. Even where all the incentives toward study excellence are present, i.e., in placebo-controlled trials, effective drugs are not necessarily demonstrably effective (i.e., superior to placebo) every time they are studied. In the absence of a placebo group, a finding of no difference in an active-control study therefore can mean that both agents are effective, that neither agent was effective in that study, or that the study was simply unable to tell effective from ineffective agents. In other words, to draw the conclusion that the test article was effective, one has to know with assurance that the active-control would have shown superior results to a placebo, had a placebo group been included in the study.

For certain drug classes, such as analgesics, antidepressants or antianxiety drugs, failure to show superiority to placebo in a given study is common. This is also often seen with antihypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these situations, active-control trials showing no difference between the new drug and control are of little value as primary evidence of effectiveness and the active-control design (the study design most often proposed as an alternative to use of a placebo) is not credible.

In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly (almost always) be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been regularly effective.

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in
interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.

For additional information, contact:

For DRUG PRODUCTS:
Drug Information Branch (HFD-211)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-4573

For a BIOLOGICAL BLOOD product, contact:
Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
301-827-3518

For a BIOLOGICAL VACCINE product, contact:
Office of Vaccines Research and Review (HFM-400)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892-0001
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:
Office of Therapeutics Research and Review (HFM-500)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1420
301-594-2860
References:

21 CFR 50.23(a)
21 CFR 50.23(c)
21 CFR 56.102(d)
21 CFR 56.102(l)
21 CFR 104(c)
21 CFR 312.36
45 CFR 46.116(f)

Procedures:

1. In instances when an investigator may be able to alert the IRB in advance of an “emergency use” of a test article, he/she must report in writing to the IRB the following:

   - A description of the circumstances that warrant the administration of a test article without IRB approval
   - A statement that the subject is confronted with a life-threatening situation that requires immediate medical intervention before the IRB can be convened.
   - Confirmation that no alternative method of approved or generally recognized therapy is available to provide an equal or greater likelihood of saving the subject's life.
   - A description of how the test article will be used.
   - A copy of the informed consent document to be used; or A statement that the informed consent document cannot be obtained because of difficulty in communication with the subject and/or insufficient time to contact the subject’s legal representative. Both the primary physician and a physician who is not participating in the clinical administration of the test article must sign this document.

Upon receipt of the report, the IRB office shall forward electronically the physician’s notification to the IRB chair or designee who will review the circumstances of the “emergency use” to verify whether it meets the conditions of the federal regulation and he/she, or the IRB office, shall so notify the physician in writing either by postal mail, electronic mail, or interoffice mail of the results of that review. The IRB office shall use this prior report to initiate tracking to ensure that the investigator files a report within the five day time-frame required by federal regulation and this policy. A
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A copy of this report shall also be provided to the signatory official (VP for Institutional Effectiveness) and the director of clinical operations. Hardcopy records of the report and any additional documentation will be retained by the IRB office.

2. Irrespective of prior IRB review of “emergency use” or whether “emergency use” occurred without IRB review, in keeping with the aforementioned requirements, the investigator must submit a report within five (5) working days following the emergency use. The report may be done via hardcopy and must include the following:

- An explanation of the use, how and when the use took place, and justification based on FDA criteria for “emergency use” including why prospective IRB review was not possible, the informed consent process, and, if applicable, how IND/IDE requirements were met.

- A copy of the properly executed (signed) informed consent document or a statement that informed consent document could not be obtained because of difficulty in communication with the patient and/or insufficient time to contact the patient’s legal representative. The report should also include follow-up information on the condition of the patient in the days after the test article has been administered. The report is to be submitted in writing and must include a copy of the consent form that was (or is about to be) signed by the subject or the subject’s authorized representative.

- If immediate use of the test article was required to preserve the subject’s life, and if time was not sufficient to obtain an independent physician’s determination that (a) the subject was confronted by a life-threatening situation necessitating the use of the test article; (b) informed consent could not be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; (c) time was not sufficient to obtain consent from the subject’s legal representative; and (d) no alternative method of approved or generally recognized therapy was available that could provide an equal or greater likelihood of saving the subject's life; then the investigator must secure within 5 working days after use of the test article the determination and evaluation by an independent physician of items a-d. One that report is secured it must also be transmitted to the IRB office.

3. The after use report will be provided to the IRB at its next convened meeting after submission of the report. The IRB will report its review of the after use report in the minutes of the convened meeting as well as in writing either electronically or via hardcopy to the principal investigator.
# Nova Southeastern University
Institutional Review Board
Policies and Procedures

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4. To obtain an emergency IND, investigators must contact the following offices.

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<tbody>
<tr>
<td>Drug Products</td>
<td>Division of Drug Information (HFD-240)</td>
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<tr>
<td></td>
<td>301-827-4570</td>
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<tr>
<td>Biological Blood Products</td>
<td>Office of Blood Research and Review (HFM-300)</td>
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<tr>
<td></td>
<td>301-827-3518</td>
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<tr>
<td>Biological Vaccine Products</td>
<td>Office of Vaccines Research (HFM-400)</td>
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<td></td>
<td>301-827-3070</td>
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<tr>
<td>On Nights and Weekends</td>
<td>Office of Crisis Management &amp; Emergency Operations Center (HFC-160)</td>
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<td>301-443-1240</td>
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