DUKE UNIVERSITY HEALTH SYSTEM
Human Research Protection Program

Expanded Access for an Investigational Medical Product for an Individual Patient, Including for Emergency Use

3/24/2021
(replaces the EMERGENCY USE POLICY)

Expanded access, sometimes called “compassionate use”, is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Requirements for All Expanded Access Uses

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), a patient may seek individual patient expanded access to investigational products for the diagnosis, monitoring, or treatment of a serious disease or condition if the following conditions are met:

- The patient and a licensed physician are both willing to participate.
- The patient's physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient’s disease or condition.
- That the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
- FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance (except for the emergency use of a medical device, which may proceed without prior FDA review).
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval;
- The sponsor (generally the company developing the investigational product for commercial use) or the clinical investigator (or the patient’s physician in the case of a single patient expanded access request) submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with FDA’s statute and applicable regulations for investigational new drug applications (INDs) or investigational device exemption applications (IDEs), describing the use of the investigational product; and
- The patient is unable to obtain the investigational product under an existing regulatory application or to participate in a clinical trial.

Physician Role in Seeking Expanded Access for an Investigational Medical Product

The physician must determine that the patient's current disease or condition is either:

- **A serious disease/condition**: a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one; or
- **Immediately life threatening**: a disease or condition is a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

The physician must also determine that there is no comparable or satisfactory alternative to diagnose, monitor, or treat the disease or condition.

If the physician has not already obtained FDA authorization of the expanded access, the IRB and/or Office of Regulatory Affairs and Quality (ORAQ) can assist in ensuring that appropriate patient protections are contemplated and will remind the physician of the reporting requirements. The IRB 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 will provide information to the investigator for how to comply with these regulations and guidance.

Non-Emergency Use Procedures

Procedures for Seeking Prospective Concurrence by IRB Chairperson

For individual patient IND:

A physician submitting an individual patient expanded access IND using Form FDA 3926 may select the appropriate box on that form to request a waiver under § 56.105 of the requirements in § 56.108(c), which relate to full IRB review. FDA concludes that such a waiver is appropriate for individual patient expanded access INDs when the physician obtains concurrence by the IRB chairperson or another designated IRB member before treatment use begins. A physician submitting an individual patient expanded access IND using Form FDA 1571 may include a separate waiver request with the application. DUHS IRB and Duke's Office of Regulatory Affairs (ORAQ) recommend that full IRB review is waived in these individual circumstances. Review will occur via IRB Chair concurrence.

For expanded access that is submitted to the FDA or deemed by the FDA to be "non-emergency", the FDA allows up to 30 days for the IND to go into effect. In practice, however, these requests are being reviewed more quickly, with IND

approval often obtained in a matter of 2-3 business days. Be aware that the investigational drug may not be administered until:

1. Documentation of the IND being in effect is provided to the IRB
2. Approval, via IRB Chair concurrence, is obtained.
3. Written, informed consent is obtained

For individual patient expanded access for a medical device

If a licensed physician would like to obtain an investigational device for an individual patient, the medical device company must first agree to provide the investigational device for compassionate use. The FDA cannot require a company to provide an investigational device for compassionate use to proceed. If the device manufacturer agrees to provide the device under compassionate use, there are two different processes to follow to obtain FDA approval, depending on whether or not there is an IDE for a clinical trial for that device. If there is an IDE for the device, the sponsor should submit an IDE supplement requesting approval for compassionate use. If there is no IDE for the device, a compassionate use request for a single patient may be submitted by the physician to the FDA. For both situations, patient protection measures should include an independent assessment from an uninvolved physician. IRB Chair concurrence should be obtained.

Procedures when Prospective IRB Chairperson Concurrence is Unable to be Obtained

Emergency Use Procedures

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 an IRB chair or designated member. For devices, because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use. When prospective IRB approval is not obtained from an IRB chairperson or designated member, the emergency use will be reported to the IRB within five working days.
4. Any subsequent use of the investigational product will have prospective IRB review and approval.
5. The use does not involve a systematic investigation designed to develop or contribute to generalizable knowledge.
6. 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.

If there is an emergency that requires the patient to be treated before a written submission can be sent to FDA, the treating physician should follow applicable FDA procedures.

> If the product is an ***investigational drug***, the treating physician should communicate the emergency use request to FDA by telephone or other rapid means of communication and wait for FDA authorization of the expanded access use before proceeding. Be aware that FDA will provide an IND number when they authorize an expanded access request. In an emergency, FDA may authorize the expanded access use to begin by telephone and the IND number may be given via telephone.
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> If the product is an ***investigational device***, the treating physician may proceed with the emergency use treatment following as many patient protection procedures as possible. FDA should be notified of the emergency use of the investigational device within 5 working days.

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

These include:

1. Informed consent from the patient or a legal representative;
2. Clearance from the institution as specified by this policy;
3. Concurrence of the IRB chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the device manufacturer.

Informed Consent Requirements

In both emergency and non-emergency expanded access situations, investigators are required to obtain the informed consent of the subject or the subject's legally authorized representative prior to administration of the investigational medical product. Informed consent must 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. One of the purposes of informed consent is to ensure that the patient is informed that he/she will be treated with an investigational product and that there may be uncertainty about the safety and effectiveness of the product.

Waiver of Informed Consent

The investigator is expected to obtain the written consent of the subject or the subject’s legally authorized representative for all expanded access cases, including emergency

use. However, if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing to 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 or 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 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 product 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 or device, have the determination reviewed and evaluated in writing by a physician who is not participating in the expanded access. The investigator must notify the IRB within five (5) business days after the use of the drug or biologic or device (21 CFR 50.23(c)).

This exemption allows for one emergency use of an investigational drug or biologic or device without prospective IRB review, provided that such an emergency use is reported to the IRB within five (5) business days. After the emergency use, 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 entity.

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 and is covered under a separate IRB policy. 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.

Specifically for Unapproved Devices:

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.

Safety Reporting, to the FDA and IRB

For INDs:
As with any IND, sponsor-investigators are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required under 21 CFR 312.

For individual patient expanded access, the regulations in § 312.310(c)(2) specify that, at the conclusion of treatment, the sponsor must provide to FDA a written summary of the results of the expanded access use, including adverse effects. With respect to reporting serious and unexpected adverse reactions in IND safety reports, under 21 CFR 312.32(c), the sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. ORAQ can assist PIs with questions regarding these submissions.

For expanded access device requests:
Following the compassionate use of the device, a follow-up report should be submitted by whomever submitted the original compassionate use request to the FDA within 45 days of using the investigational device. This report should present summary information regarding patient outcome. If any problems occurred as a result of device use, these should be discussed in the follow-up report and reported to the reviewing IRB as soon as possible.

Regarding reporting events to the IRB, investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems.

In general, an AE observed during the expanded access should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the expanded

access use (e.g., requiring a significant, and usually safety-related, change in the treatment plan. An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

References:

FDA guidance on "Expanded Access to Investigational Drugs for Treatment Use": https://www.fda.gov/media/85675/download

https://www.fda.gov/news-events/public-health-focus/expanded-access

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

For DUHS support for single patient INDs, please visit this resource: https://medschool.duke.edu/research/research-support-offices/office-regulatory-affairs-and-quality/individual-patient-ind-support

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