Human Subject Protection Program
Investigator Guidance
May 22, 2020

EXPANDED ACCESS AND EMERGENCY USE OF A TEST ARTICLE (DRUG, BIOLOGIC OR DEVICE)

Expanded Access to Investigational Drugs or Biologics

- Under FDA regulations, expanded access allows for the use of unapproved drugs and biologics outside of a clinical trial.
  - ☐ This is sometimes also called **compassionate use or treatment use**.

☐ FDA submission and IRB review are required for expanded access.

Expanded Access to Unapproved Devices

- Expanded access is a way for patients with a serious or life-threatening disease or condition to get access to an investigational medical device that has not been approved or cleared by the FDA for treatment outside of clinical trials.

Definitions:

- **Immediately life-threatening disease or condition** means 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.

- **Serious disease or condition** means 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.

- **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 patients 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.

- **IND** - An Investigational New Drug Application is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans.

- **IDE** - An approved investigational device exemption permits a device that otherwise would be required to comply with a performance standard or to have premarket

approval to be shipped lawfully for the purpose of conducting investigations of that device.

- **Unapproved medical device** is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e)(the act) or an approved IDE under section 520(g) of the act (21 U.S.C. 360j(g)).

FDA Criteria for All Expanded Access Uses of Investigational Drugs and Biologics

The FDA needs to determine that:

- The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

- The potential benefit to the patient justifies the potential risks of the treatment and the potential risks are not unreasonable in the context of the disease or condition to be treated; and

- Providing the investigational drug for the requested use will not interfere with clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Types of Expanded Access Programs for Drugs and Biologics

Single Patient Expanded Access - Non-Emergency Use

- The following criteria need to be met in addition to those for all expanded access uses noted above:

  - ☐ The physician needs to determine that the probable risk to the patient from the investigational drug is no greater than the probable risk from the disease or condition; and

  - ☐ The FDA needs to determine that the patient cannot obtain the drug under another IND or protocol.

- If there is an existing IND for the drug, the expanded access IND submission to the FDA is made by the sponsor or a physician.

- Physicians should use Form FDA 3926 to request expanded access to an investigational drug outside of a clinical investigation. The FDA provides guidance on How to Request Single Patient Expanded Access.

- The treating physician should submit the proposed non-emergency use to the CHLA IRB for expedited review in iStar.

  - ☐ A new study application should be created by the physician by clicking on the "New Emergency Use/Expanded Access Application" tab in iStar.

  - ☐ The abbreviated submission for "Expanded Access (Compassionate Use)" for a drug/biologic should then be completed by the physician. Copies of the documentation submitted to the FDA (e.g. Form 3926) as well as a consent form for the single patient to be treated should be submitted (uploaded) within the iStar application.

Single Patient Expanded Access - Emergency Use

- When there is an immediately life-threatening situation and insufficient time for IRB review, the treating physician may exercise the Emergency Exemption from Prospective IRB Approval. See the Emergency Use of an Investigational Drug or Biologic FDA Information Sheet for detailed information and contacts.

- **The FDA emergency use provision is an exemption from prospective IRB review and approval for one emergency use of a drug or biologic.**

  - ☐ The FDA requires that IRB review and approval is obtained before **any subsequent use** of a drug or biologic occurs, although they acknowledge that it would be inappropriate to deny emergency treatment to a second individual due to insufficient time for IRB review.

- The FDA provides an Emergency IND Timeline for Submission of Single Patient Application for Emergency Use.

- Whenever possible, the CHLA IRB should be notified in advance of the proposed emergency use of an unapproved drug or biologic.

- If the Emergency Exemption is exercised, the treating physician needs to immediately notify the CHLA IRB.
  - ☐ A new study application should be created by the physician by clicking on the "New Emergency Use/Expanded Access Application" tab in iStar.
  - ☐ The abbreviated submission for "Emergency Use" of a drug/biologic should then be completed by the physician. There is an option to notify the IRB prior to the use.
  - ☐ Regardless of whether the IRB is notified in advance of the proposed emergency use, the treating physician needs to **complete a 5-day Report in iStar** so that the IRB can make certain that the use was appropriate.

- The physician also needs to report the use and any adverse events to the FDA.

Expanded Access for Intermediate Size Populations

- The FDA may permit an investigational drug to be used for treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. In cases where FDA has received a significant number of requests for individual patient expanded access for the same use, a sponsor may be asked to consolidate expanded access under this category.

- In addition to the criteria listed at the beginning of this section for all expanded access, the FDA needs to determine that there is enough evidence that the drug is safe at the proposed dose and duration and there is at least preliminary evidence of effectiveness of the drug as a therapeutic option in the patient population. For more information about FDA requirements, please see 21 CFR 312.315.

- Intermediate size expanded access protocols need to be submitted through the usual IRB process and require full IRB review and approval under FDA regulations.

Expanded Access for Large Patient Populations

- Expanded access protocols for large patient populations are also called treatment IND or treatment protocols. This category is used for widespread treatment use of an investigational drug.

- In addition to the criteria listed at the beginning of this section for all expanded access, the FDA needs to determine:
  - ☐ That the drug is being investigated in a controlled trial under an IND to support a marketing application for the expanded access, or
  - ☐ All clinical trials of the drug have been completed;
  - ☐ The sponsor is actively pursuing marketing for approval of the expanded access; and
  - ☐ There is sufficient data supporting safety and effectiveness of the drug for the expanded access.
- Expanded access protocols for large patient populations need to be submitted per the usual IRB process and require full IRB review and approval under FDA regulations.

Expanded Access to Unapproved Devices

Emergency Use of an Unapproved Device

- An unapproved device should normally only be used in human subjects if it is approved and used for clinical testing under an IDE. However, emergency use of an unapproved device may also occur:
  - ☐ When an IDE for the device does not exist;
  - ☐ When a physician wants to use the device in a way not approved under the IDE; or
  - ☐ When a physician is not an investigator under the IDE. The sponsor needs to notify the FDA within 5 days through submission of an IDE report describing the case and the patient protection measures that were followed.

FDA Criteria for Emergency Use of a Device

- The physician that will use the device needs to determine that the following criteria are met:

- ☐ The patient has a life-threatening or serious disease or condition that needs immediate treatment;

- ☐ There is no generally acceptable alternative treatment for the condition;

- ☐ Because of the immediate need to use the device, there is no time to obtain FDA approval.

- The FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device and to have substantial reason to believe that benefits will exist.

- Under the emergency use provisions, the emergency use of an unapproved device is an exemption from prior review and approval by the IRB but **must be reported to the IRB within 5 working days**.

- FDA guidance indicates that the physician should follow as many patient protection procedures as possible, including:

  - ☐ Informed consent from the patient or a legal representative;

  - ☐ Clearance from the institution as specified by their policies;

  - ☐ Concurrence of the IRB Chair or another Designated IRB Member;

  - ☐ An independent assessment from an uninvolved physician; and

  - ☐ Authorization from the IDE sponsor, if an approved IDE exists.

- The treating physician should submit the expanded access use to the CHLA IRB for expedited review in iStar.

  - ☐ A new study application should be created by the physician by clicking on the "New Emergency Use/Expanded Access Application" tab in iStar.

  - ☐ The abbreviated submission for "Expanded Access" of a device should then be completed by the physician.

  - ☐ There is an option to notify the IRB prior to the use.

- ☐ Regardless of whether an initial notification is submitted, the physician needs to complete a 5-day Report in iStar so that the IRB can determine that the use was appropriate.

- The physician also needs to report the use and any adverse events to the FDA.

- If there is an IDE for the device, the IDE sponsor needs to 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 the device used, details of the case, and the patient protection measures that were followed.

  - ☐ **Subsequent emergency use of the device may not occur** unless the physician or another person obtains approval of an IDE for the device and its use.

Compassionate Use (or Single Patient/Small Group Access)

- FDA's compassionate use provision allows access to an unapproved device for patients who are not eligible for a particular clinical trial but for whom the device may provide a benefit in treating and/or diagnosing their disease or condition. Compassionate use may be used only during the clinical trial for which the device is being tested. Compassionate use may be approved for a single patient or a small group of patients. Criteria:

  - ☐ The device is intended to treat or diagnose a serious disease or condition; and

  - ☐ There is no comparable or satisfactory alternative device or therapy available.

- FDA approval is required before compassionate use occurs. The sponsor of the IDE is required to submit an IDE supplement requesting approval under 812.35(a) in order to treat the patient. For further instructions about FDA requirements for the IDE supplement, please refer to Expanded Access for Medical Devices.

- The physician may not treat the patient until FDA approves the compassionate use for the intended patient. FDA will consider preliminary evidence of safety and effectiveness as well as whether the compassionate use would interfere with the conduct of a clinical trial to support marketing approval.

- Once approved, the patient should be monitored for safety. Follow up information on the use of the device should be submitted in an IDE Report after compassionate use has ended.

- Expanded access protocols for devices need to be submitted per the usual IRB process and require full IRB review and approval under FDA regulations.

Informed Consent Requirements

- Every effort should be made to obtain informed consent from the patient before the emergency use of a drug or device. If written informed consent is not possible, there are special provisions for an informed consent waiver.

- Whether the physician creates 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 CHLA template but need not follow the CHLA format and wording. It should be clearly stated 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 should be included in the post-use written report.

- **Waiver of Consent:** If prior consent is not possible, federal regulations allow a waiver under the following conditions:

  - ☐ Before the test article is used, both the treating physician and an independent physician who is not otherwise participating in the clinical investigation must certify in writing all of the following:

- ✓ The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- ✓ Informed consent cannot be obtained from the subject 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.
- ✓ There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

☐ If immediate use of the test article is required to preserve the life of the subject, and time is not sufficient to obtain an independent physician's assessment, the determinations of the treating physician should be made and reviewed and evaluated in writing by an independent physician within 5 working days after the use of the article.

☐ The documentation outlined above should be submitted to the IRB within 5 working days after the use of the test article.

FDA Resources

- 21 CFR 312: Subpart I – FDA regulations for all types of expanded access to investigational drugs for treatment use, including emergency use.
- Expanded Access to Investigational Drugs for Treatment Use - Qs & As
- Exception from Informed Consent Requirements for Emergency Research FDA Guidance
- 21 CFR 812.36 Treatment use of an Investigational Device
- Expanded Access for Medical Devices
- Emergency and Compassionate Use of Unapproved Devices (lecture presented by Dr. F. Santel at CDRH, FDA)