The Christ Hospital IRB
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IRB REFERENCE MANUAL
SECTION 13
EXPANDED ACCESS TO INVESTIGATIONAL MEDICAL PRODUCTS

Note: Federal regulations related to expanded access to investigational medical products are in 21 CFR 56 (sec 102d, 104), 21 CFR 50 (sec 23), 21 CFR 312 (sec 36), 21 CFR 812.

13.0 EXPANDED ACCESS TO INVESTIGATIONAL MEDICAL PRODUCTS

13.1 INVESTIGATIONAL DEVICES

An unapproved medical device may normally only be used on human subjects through an approved clinical study in which the subjects meet certain criteria and the device is only used in accordance with the approved protocol by a clinical investigator participating in the clinical trial. However, there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. Patients/physicians faced with these circumstances may have access to investigational devices under one of four mechanisms by which FDA may makes an unapproved device available:

- Emergency Use
- Compassionate Use (or Individual Patient/Small Group Access)
- Treatment Investigational Device Exemption (IDE)
- Continued Access

These mechanisms can be utilized during a certain timeframe in the IDE process if the criteria are met. FDA approval is required except in the case of emergency use. The mechanisms are summarized below:

13.1.1 Emergency Use:

Emergency situations may arise in which there will be a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Emergency use of an unapproved device may occur before an IDE is approved.

Criteria:

- Life-threatening or serious disease or condition
- No alternative
- No time to use existing procedures to get FDA approval for the use

Timeframe: Before or after initiation of the clinical trial

There are special cases under emergency research in which the human subject is in a life-threatening situation, and it is not feasible to obtain informed consent. In order to allow such research to proceed, special provisions for exception from informed consent requirements, must be met. (Guidance concerning waiver of consent requirements for certain emergency use under FDA regulations can be found on their website or at Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research | FDA. In addition, the IRB and a physician not participating in the investigation must review and concur with the use. The sponsor must also submit a separate IDE application to FDA.

Documentation must be provided to the FDA within 5 working days after sponsor learns of the use. The report should include circumstances of the case and patient protection measures followed, including:

- informed consent,
- institutional clearance,
- concurrence of IRB Chairperson,
- independent assessment from an uninvolved physician,
- authorization from IDE sponsor (if IDE exists) or manufacturer.
- Monitoring plan and follow-up information is to be provided to the FDA.

13.1.2 Compassionate Use (or Individual Patient/Small Group Access):

The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation, but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients; however may be approved to treat a small group.

Criteria:

- Serious disease or condition
- No alternative

Timeframe: During clinical trial

The FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, but not life-threatening, disease or condition. In these circumstances, the FDA uses its regulatory discretion in determining whether such use of an investigational device should occur.

Prior FDA approval is needed before compassionate use occurs (30 calendar day review timeframe). In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol

deviation under section 812.35(a) in order to treat the patient. The IDE supplement should include:
Description of patient's condition and circumstances necessitating treatment;

- A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is not greater than the probable risk from the disease or condition;
- Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient, and;
- The patient protection measures that will be followed:
    - informed consent,
    - concurrence of IRB Chair,
    - clearance from the institution,
    - independent assessment from uninvolved physician,
    - authorization from IDE sponsor.

The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to the FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from a serious disease or condition for which no alternative therapy adequately meets their medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

13.1.3 Treatment Use:

An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.

Criteria:

- The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
- There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
- The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
- The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

Time-frame: During clinical trial.

A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable, or satisfactory alternative device, or other therapy, is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the treatment investigational device exemptions (IDE) regulation (812.36).

The treatment use provision of the IDE facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials.

An "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. "Treatment use" of a device includes the use of a device for diagnostic purposes.

Applications for Treatment Use: A treatment IDE application must include, in the following order:

- Name, address and telephone number of the sponsor of the treatment IDE;
- Intended use of the device, criteria for patient selection, and a written protocol describing the treatment use;
- Explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
- Description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
- Written procedures for monitoring the treatment use and the name and address of the monitor;
- Instructions for use for the device and all other labeling as required under section 812.5(a) and (b);
- Information that is relevant to the safety and effectiveness of the device for the intended treatment use;
- A statement of the sponsor's commitment to meet all applicable responsibilities under the IDE regulations (21 CFR 812) and IRBs regulations (212 CFR 56) and to ensure compliance of all participating investigators with the informed consent requirements of 21 CFR 50;
- An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
- If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56.

Applications should be identified on the outside envelope as a treatment IDE application and reference the IDE number. The original and two copies should be mailed to the following address:
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center (DCC) – WO66-G609

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA Action on Treatment IDE Applications

a. Approval of Treatment IDE's: Treatment use may begin 30 days after FDA receives the treatment IDE submission. FDA may notify the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.
b. Disapproval or withdrawal of approval of treatment IDE's: FDA may disapprove or withdraw approval of a treatment IDE if:
    1. The required criteria [812.36(b)] are not met or the treatment IDE application does not contain the required information [812.36(c)].
    2. FDA determines that any of the grounds for disapproval or withdrawal of approval apply [812.30(b)(1)] through (b)(5)].
    3. The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;
    4. The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:
        - may be effective for its intended use in its intended population; or
        - would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury.
    5. There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;
    6. The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being use;
    7. The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;
    8. Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or
    9. The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

c. Notice of Disapproval or Withdrawal: If the FDA disapproves or proposes to withdraw approval of a treatment IDE, the FDA will follow the procedures set forth in the IDE regulations [812.30(c)].

Safeguards: Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (21 CFR 50) and IRB's (21 CFR 56).

Reporting Requirements: The sponsor of a treatment IDE must submit progress reports on a semi-annual basis to all reviewing IRB's and FDA p until the filing of a marketing application. The date of these reports are based on the period of time since initial approval of the treatment IDE. A*fter* filing of a marketing application, progress reports must be submitted annually in accordance with the IDE regulation. The progress report must also include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device.

The sponsor of a treatment IDE is responsible for submitting all other reports required under 812.150 (Reports), such as unanticipated adverse device effects and final reports. The reports are submitted as supplements to the original IDE application.

13.1.4 Continued Access:

The FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by the FDA.

Criteria:

- Public health need, or
- Preliminary evidence that the device will be effective and there are no significant safety concerns.

Timeframe: After completion of the clinical trial.

The sponsor of a clinical investigation is permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor and/or reviewed by the Agency if there is:

- a public health need for the device; or
- Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

The continued enrollment of subjects in an investigation while a marketing application is being prepared by the sponsor and/or reviewed by ODE is known as an "extended investigation." Extended investigations permit patients and/or physicians continued access to the devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. The Continued Access Policy may be applied to any clinical investigation that meets the criteria identified above; however, it is intended to be applied late in the device development process, i.e., after the controlled clinical trial has been completed.

A sponsor's request for an extended investigation should be submitted as an IDE supplement and include the following information:

- Justification for the extension;
- Summary of the preliminary safety and effectiveness data generated under the IDE;
- A brief discussion of the risks posed by the device;
- The proposed rate of continued enrollment (the number of sites and subjects);
- The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
- A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device.

There is significant overlap between the treatment IDE regulation and the Continued Access Policy. Both the Continued Access Policy and the treatment IDE regulation are intended to provide additional access to an unapproved device, once preliminary evidence regarding safety and effectiveness is available to the FDA. However, because a treatment IDE can be submitted earlier in the IDE process, i.e., once promising evidence of safety and effectiveness has been collected under the IDE but while the clinical study is ongoing, it could provide access to a wider group of patients at an earlier stage in the IDE process. The treatment IDE regulation also has a more narrow application than the Continued Access Policy in that treatment use is intended to address only those patients who have an immediately life-threatening or serious disease or condition whereas the Continued Access Policy, which is applied after completion of the clinical trial, may be considered for any clinical investigation.

13.2 INVESTIGATIONAL DRUGS AND BIOLOGICS

The FDA Expanded Access (EA) program allows for compassionate use for treatment purposes in patients with serious diseases or conditions when there are no comparable or satisfactory alternative therapies to diagnose, monitor or treat the

patient's disease or condition and the sponsor or manufacturer agrees to provide the drug for treatment purposes.

FDA describes three distinct categories of expanded access based on the number of people who need access and the level of risk. An expanded access IND submission is required for each type of expanded access. The submission may be a *new IND* or a protocol amendment to an *existing IND*.

13.2.1 Individual Patient IND, including Emergency Use IND [21 CFR 312.310] - commonly held by treating physician or investigator for treatment of an individual patient.

13.2.1.1 Individual Patient Expanded Access IND Treatment or Protocol

- Access to an investigational drug (including a biologic) for use by a single patient submitted as a protocol *under a new IND*. The investigational product may or may not be under development. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment with the drug may begin.
- Access to an investigational drug (including a biologic) for use by a single patient submitted as a new protocol *to an existing IND by the sponsor of the existing IND*. Typically, several patients may follow the same protocol. The investigational product may or may not be under development. There is no 30-day waiting period before treatment with the investigational product may begin, but the protocol must be received by FDA and have approval by the IRB before treatment may begin.

13.2.1.2 Individual Patient Access in an Emergency

- Emergency IND: Individual Patient Access IND for Emergency use: Access to an investigational drug (including a biologic) for use by a single patient in an emergency situation (i.e., a situation that requires a patient to be treated before a written submission can be made) submitted as a protocol under a new IND. Treatment is initially requested and authorized by telephone or other rapid means of electronic communication, and may start immediately upon FDA authorization. The written submission (i.e., the individual patient expanded access IND) must be submitted within 15 business days of the telephone authorization.
- Emergency Protocol: Individual Patient Expanded Access Protocol for Emergency Use: Access to an

investigational drug (including a biologic) for use by a single patient in an emergency situation (i.e., a situation that requires a patient to be treated before a written submission can be made) submitted as a new protocol to an existing IND by the sponsor of the existing IND. Treatment is initially requested and authorized by telephone or other rapid means of communication, and treatment may start immediately upon FDA authorization. The written submission (i.e., the individual patient expanded access protocol) must be submitted within 15 business days of the telephone authorization.

In an emergency situation where there is not sufficient time to secure IRB review prior to beginning treatment, the emergency use of the investigational drug must be reported to the IRB within 5 working days, as required under 21 CFR 56.104(c).

Access to an investigational drug (including a biologic) for use by a single patient submitted as a new protocol *to an existing IND by the sponsor of the existing IND*. Typically, several patients may follow the same protocol. The investigational product may or may not be under development. There is no 30- day waiting period before treatment with the investigational product may begin, but the protocol must be received by FDA and have approval by the IRB before treatment may begin.

13.2.2 Intermediate Population Treatment IND or Treatment Protocol [21 CFR 312.315] – commonly held by the sponsor (manufacturer) for use in population smaller than typical of treatment IND or treatment protocol. The investigational product may or may not be under development for marketing. The difference between a Treatment IND and Treatment Protocol is that there is a 30-day waiting period before treatment may begin with a Treatment IND. However, with a Treatment Protocol, the protocol must be received by FDA and have IRB approval before treatment may begin.

13.2.3 Large Population Treatment IND or Treatment Protocol [21 CFR 312.320] – commonly held by the sponsor for widespread treatment use. The sponsor must be pursuing marketing approval. The difference between a Treatment IND and Treatment Protocol is that a Treatment IND must be submitted under *a new IND*, a Treatment Protocol can be submitted as a protocol to *an existing IND by the sponsor of an existing IND*. There is a 30-day waiting period before treatment may begin with a both a Treatment IND and a

Treatment Protocol, unless the FDA notifies the sponsor that treatment may begin earlier in the case of a Treatment Protocol.

A treatment IND may be granted only after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. In addition, the following criteria must be met:

- The drug must be 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, and
- The trial sponsor is actively pursuing marketing approval.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced case of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the safety and effectiveness of the drugs in question.