

CARILION CLINIC INSTITUTIONAL REVIEW BOARD

Standard Operating Guidelines

Title: 4.2: Investigational Devices: INVESTIGATIONAL DEVICE EXEMPTION, SIGNIFICANT/NON-SIGNIFICANT RISK DEVICES, HUMANITARIAN USE DEVICES, EMERGENCY USE, COMPASSIONATE USE	
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Objective:

To set forth guidance from the Carilion Institutional Review Board (IRB) regarding review and approval of the use of investigational medical devices, including emergency and compassionate use of medical devices, and Humanitarian Use Devices (HUD).

General Description:

Clinical investigations of medical devices must comply with the Food and Drug Administration (FDA) regulations, along with IRB regulations. Research studies intending to evaluate the safety and/or efficacy of an investigational medical device must be conducted in compliance with 21 CFR 812.

When a research study is designed to test safety or effectiveness of an investigational device, the IRB is responsible for verifying that the study has a valid Investigational Device Exemption (IDE) approval issued by the FDA, or qualify for an *abbreviated* IDE (21 CFR 812.2(b)), or qualify for an IDE *exemption* (21 CFR 812.2(c)). When an IDE is required, the IRB must make a Significant Risk/Non-Significant Risk determination regarding the device, unless this determination has already been made by the FDA.

The FDA does recognize that situations may arise in which there will be a need to use an investigational device in a manner inconsistent with an investigational plan. These exceptions must meet specific criteria, which are outlined in this document.

All device uses subject to this policy will be reviewed or reported to the Carilion IRB and other appropriate institutional officials as applicable.

Investigational Device Exemption (IDE) Requirements

When an investigational device does not meet the requirements for an IDE *exemption* or an *abbreviated* IDE, a study may only be approved when the FDA has issued an Investigational Device Exemption (IDE). An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE 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. Investigators who submit to the IRB before submitting to the FDA may be asked to withdraw their IRB submission and resubmit after the IDE has been obtained.

An IDE is considered approved 30 days after the FDA receives the application, although the sponsor may receive earlier notification of approval.

At least one of the following should be used for IDE verification:

- A study protocol, as submitted to the FDA, including an IDE number
- Communication from the FDA with verification of the IDE
- When the IDE is held by the sponsor:
 - A sponsor's protocol specifying the IDE number
 - Communication from the sponsor verifying the IDE number

Abbreviated IDE Requirements

The FDA considers an investigational device to have an approved application for an abbreviated IDE when a device is a Nonsignificant Risk (NSR) device that is not banned and the sponsor does the following:

1. Labels the device in accordance with 812.5;
2. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not an SR device, and maintains such approval;
3. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under 21 CFR 50 and documents it, unless documentation is waived by an IRB under 56.109(c);
4. Complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
5. Maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b)(1) through (3) and (5) through (10);
6. Ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.159(a)(1), (2), (5), and (7); and
7. Complies with the prohibitions in 812.7 against promotion and other practices.

Investigations Exempted from the Investigational Device Exemption (IDE) Requirements

21 CFR 812 Investigational Device Exemption (IDE) requirements are not applicable when the device meets one of the exemption categories below:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time. [i.e., a legally marketed device when used in accordance with its labeling]
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence. [i.e., a legally marketed device when used in accordance with its labeling]
3. A diagnostic device, if the sponsor complies with applicable requirements of 809.10(c) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,
 - c. Does not by design or intention introduce energy into a subject, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety and effectiveness and does not put subjects at risk.

5. A device intended solely for veterinary use.
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
7. A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. The use of custom devices will require IRB review if the use meets the definition of human subjects research according to the regulations.

510(k) Device Studies May be Conducted Without an IDE

The FDA notes that a premarket notification, or 510(k), is submitted to the FDA before a manufacturer proposes to market a medical device. If the FDA agrees the new device is substantially equivalent to a legally marketed device for which premarket approval is not required, the manufacturer may market the device immediately. The FDA does not require clinical data on most 510(k)s. The exemption in 21 CFR 812.2(c)(2) applies only to investigations in which the 510(k) product is being used in accordance with the labeling clearly by the FDA. However, if clinical data are necessary to demonstrate substantial equivalence, the clinical study must comply with the IDE, IRB and human subjects protection regulations. Further, "off-label" use of a 510(k) product take the product outside the exemption. A device subject to 510(k) remains investigational until the 510(k) is cleared by the FDA and the investigational use is subject to the requirements of the IDE, IRB and human subjects protection regulations [21 CFR 812, 50, and 56].

Significant Risk (SR) vs. Nonsignificant Risk (NSR) Medical Device Studies

Federal regulations define a significant risk (SR) device investigation as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and:

- Is an implant; or
- Is used in supporting or sustaining human life; or
- Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

SR devices include such things as pacemakers, urological stints, electroconvulsive therapy devices, diaphragms, implantable prostheses, surgical lasers and tracheal tubes.

A nonsignificant risk (NSR) device investigation is one that does not meet the above stated definition for a significant risk device investigation. NSR device investigations, however, should not be confused with the concept of "minimal risk," a term used in IRB regulations to identify certain studies that may be approved through an expedited review procedure.

NSR devices include such things as low power lasers for treatment of pain, daily wear contact lenses, jaundice monitors for infants, wound dressings, and Foley catheters. A more comprehensive lists of significant and nonsignificant devices has been compiled by the FDA's Center for Devices and Radiological Health.

The effect of the SR versus NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR Part 812]. NSR device studies have fewer regulatory controls and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the

record keeping and reporting requirements. The SR versus NSR decision is also important to the FDA because the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies. The IRB may utilize different types of information in the risk determination. This may include a detailed description of the device and reports of prior investigations using the device. If requested, the IRB should be informed about whether other IRBs have reviewed the proposed study and what risk determination was made. The IRB may also consult with the FDA for its opinion. The FDA has the ultimate decision in determining if a device is SR or NSR. If the FDA does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. The FDA is usually not apprised of the existence of approved NSR studies; sponsors and IRBs are not required to report NSR device study approvals to the FDA.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continued review by the IRB is required. A Research Submission Application, consent form, and supporting documentation should be submitted to the Carilion IRB for consideration of approval of a SR or NSR device study. The submission will then be processed in accordance with Carilion IRB Guideline 2.1.

The FDA considers studies of all SR devices to present more than minimal risk and must undergo full board review. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk and the IRB may choose to review those studies under its expedited review procedures.

When a sponsor believes an investigational device is an NSR device, a risk assessment and the rationale used to make this determination should be provided to the Carilion IRB. The IRB may request additional information from the sponsor, such as a description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. Additionally, the sponsor should advise the IRB of any determinations made by other IRBs, and the determination made by the FDA, if applicable. The Carilion IRB may consult with the FDA. The IRB will include in its minutes any determination made about whether a device study is a SR or NSR device study.

If the Carilion IRB agrees that the device investigation is NSR and approves the study, the investigation may begin at that institution immediately, without the submission of an IDE application to the FDA.

If the Carilion IRB determines that the proposed device study is SR, then the IRB will inform the sponsor of its determination in writing. The sponsor is required to inform the FDA of this determination. If the FDA agrees that the investigation presents a significant risk, then the investigation may not proceed without first obtaining FDA approval of an IDE application. If the FDA does not believe the investigation presents a significant risk, then the Carilion IRB will decide if it wants the study to proceed at its institution as a non-significant risk study.

The Carilion IRB will base its risk determination on the proposed use of a device in a study and not on the device alone. In deciding if a study proposes a SR, the IRB will consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure, should be considered SR. Also, if a subject must undergo a procedure as part of the study, e.g.

a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to potential harm caused by the device.

Also see FDA Information Sheet: "Significant Risk and Nonsignificant Risk Medical Device Studies."

Investigational Devices and their Use Outside of Research

Humanitarian Use Devices (HUD)

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [21 CFR 814.3(n)]. The purpose of the HUD program is to provide incentive for manufacturers to develop devices to diagnose or treat conditions that affect fewer than 8,000 people in the United States per year because research and development costs for so few patients can easily exceed market return.

A manufacturer receives an HUD designation for a device by submitting to the FDA a Humanitarian Device Exemption (HDE) application. A summary of safety and probable benefit is required in this application and this summary must give the FDA enough information to determine that the benefits of the device outweigh the risks. Additionally, applicants must show that no other comparable devices are available to treat or diagnose this condition.

Before an HUD can be used at any Carilion Clinic facilities, it must be approved as outlined below.

Research vs. Clinical Use of an HUD

The use of an HUD in accordance with the terms of the approved HDE and labeling for the HUD is not considered "research" as defined by the FDA. Rather, use of the HUD would be a clinical use of an approved device. However, FDA regulations require that IRB approval be obtained before the device can be used at a facility. Physicians wanting to use at HUD within the restrictions of its approved labeling should submit a Humanitarian Use Device Application to the IRB.

When safety and effectiveness data about an HUD is collected, this is considered a "clinical investigation" by the FDA. Such a study also would require submission of a research application to the IRB. FDA does not require this type of research to obtain an Investigational Device Exemption (IDE) if the HUD is being used in accordance with approved indications described in labeling.

Collection of data which will be used for a new use of the HUD is also considered a clinical investigation by the FDA. This type of research does require that an IDE be obtained from the FDA. Such a study also would require submission of a research application to the IRB.

IRB Review of an HUD

The initial review of an HUD is to be completed by the convened IRB. The IRB will review materials submitted by a physician who has principal responsibility for use of the HUD at the facility. In addition to the IRB HUD application, these materials shall include: 1) The generic and

trade name of the device 2) The FDA HDE number 3) The date of HUD designation 4) Indications for use of the device 5) A description of the device 6) Contraindications, warnings and precautions for use of the device 7) Adverse effects of the device on health 8) Alternative practices and procedures 9) Marketing history 10) Summary of studies using the devices 11) The HUD brochure 12) A patient information packet, if available from the sponsor 13) An HUD Clinical Consent Form.

The entire board receives copies of the HUD Application as well as the patient information packet/brochure and the HUD Clinical Consent Form. All items above are provided to the primary reviewers. All members will have access to the complete protocol file.

IRB review of the HUD submission will include evaluating whether risks described in the product labeling have been minimized, evaluating whether risks are reasonable in relation to the anticipated benefits of the proposed use of the device and determining whether there needs to be a plan to monitor the safety of subjects. The IRB will verify that the proposed use of the HUD corresponds with the current labeling and does not exceed the scope of the FDA-approved indication. The IRB will evaluate whether the principal responsible physician and other physicians seeking to use the device are qualified through training and expertise. The IRB should verify that the HUD is stored in a secure manner and labeled appropriately to prevent use by unapproved personnel or the use of the device in an unapproved manner.

The IRB may approve use of the HUD without any restrictions beyond the FDA-approved labeling or may impose more stringent criteria for use of the HUD as deemed necessary to provide additional protections. The use of the HUD should be restricted to personnel listed on the HUD application reviewed and approved by the IRB.

The convened board may make the determination at initial review that continuing review may occur using the expedited procedure if the HUD is not being used in the course of a research study. Continuing review of use of the HUD should occur at intervals appropriate to the degree of risk but not less than once a year. Criteria the IRB may use to grant continuing review using the expedited criteria include: initial use of the HUD was approved without further restrictions and the continuing review period was not less than a year. Continuing review of the HUD should follow the Carilion Clinic SOG on continuing review. It should be submitted on the IRB Continuing Review Application.

For initial and continuing approval of an HUD, the IRB approval letter will contain the following:

- Name and number of the HDE that is being approved
- A specific statement of the approved indications for the device
- The specific physician (or physicians) approved to use the device
- The facilities where the device may be used
- Any specific reporting requirements that are in addition to the FDA's requirements

Informed Consent for HUDs

Informed consent and documentation of informed consent is required when treating or diagnosing a patient with an HUD. When an FDA-approved patient information labeling or packet is available, this should be reviewed with the patient prior to use of the HUD. In addition, the patient should sign an IRB Patient Information Form which documents that the patient has reviewed the information packet and has had all questions answered about use of the HUD.

When the use of an HUD is for diagnosis or treatment, and not associated with research or data collection, HIPAA regulations for research are not applicable. However, HIPAA regulations for hospital medical records per institutional policy are applicable. If an HUD is being used in a clinical investigation, whether or not the HUD is the subject of the investigation, then HIPAA regulations for research apply.

Reports to the IRB

Whenever the primary responsible physician or collaborating physician receives or otherwise becomes aware of information that reasonably suggests that a device with an approved HDE under his/her use: (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur, then the physician must report these findings to the FDA and IRB as soon as practicable but no more than 10 working days after the day that the physician becomes aware of information. Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

All FDA actions and any changes to the FDA-approved indication for the use of the HUD must be submitted for IRB review using the Carilion Clinic IRB Change/Update form. The form should be accompanied by the FDA's approval of the modification, the HDE holder's amendments to the HUD product labeling, clinical brochure or other pertinent materials relating to the requested modification. The primary responsible physician should report these to the IRB as soon as practicable but no more than 10 working days after becoming aware of the modification or changes.

Off-Label Use and Emergency Use of an HUD

An HUD may be used "off-label" for clinical care if a physician approved to use the device determines there is no alternative device for the patient's condition. The physician should obtain informed consent from the patient or his/her legally authorized representative. The physician should notify the IRB about the off-label use within 7 working days of the use. The notification should include the circumstances necessitating the use of the device and the reasons why alternative therapies or diagnostics were unsatisfactory. It should also note how the patient will be monitored for any adverse effects.

If an emergency situation arises in which approval from the IRB cannot be obtained in time to prevent serious harm or death to a patient, an HUD may be administered without prior approval by the IRB. In such an emergency situation, an HUD may be used off-label to save the life or protect the physical well-being of a patient; however, in this situation, FDA recommends that the clinician and HDE holder follow the same emergency use procedures that govern the use of unapproved devices. See the section on emergency use below. Additionally, before the device is used, if possible, the physician should obtain the IRB chairperson's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. Authorization from the HDE holder is also needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit an Expanded Access Medical Devices Form to the Carilion IRB, and include information on the patient's condition and the patient protection measures to the HDE holder. See section below on emergency use for more information.

Expanded Access to Unapproved Devices

An unapproved medical device is defined as 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 FD&C Act FDA [21 USC 360(e)] or an approved IDE under section 520(g) of the Act [21 USC 360(g)]. Regulations state that an unapproved medical device may only be used on human subjects when the device is under clinical investigation and when used by investigators participating in clinical trials. However, there are four main mechanisms by which the FDA may make unapproved devices available to patients/physicians faced with special circumstances (i.e., to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no other alternative therapy). The four mechanisms are described below.

1. Emergency Use of Unapproved Medical Devices

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. Regulations permit deviations from the investigational plan when necessary to protect the life or physical well-being of a patient in an emergency. Prior approval for shipment or emergency use of the investigational device is not required, but the use should be reported to the FDA by the sponsor within five working days from the time the sponsor learns of the use. A summary of the conditions constituting the emergency, the patient protection measures and the patient outcome information should be included in this report.

A physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that:

- The patient has a life-threatening condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use

The physician should make the determination that the patient's circumstances meet the above criteria, assess the potential for benefit from using the unapproved device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an emergency exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. The local physician should follow as many patient protection procedures as possible, such as:

- Informed consent from the patient or a legal representative
- Concurrence of the IRB chairperson
- An independent assessment from an uninvolved physician; and
- Authorization from the IDE sponsor, if an approved IDE exists

After the emergency use occurs, the treating physician is responsible for follow-up procedures:

- Report the use of the device to the Carilion IRB within five days, using an Expanded Access Medical Devices Form. Include a description of the patient's response to the treatment.
- Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use.
- If an IDE exists, provide the sponsor with patient follow-up information.

- If no IDE exists, submit a follow-up report on the use of the device to the IDE staff. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

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. If an IDE application for subsequent use has been filed with the FDA and the FDA disapproves it, the device may not be used even if the circumstances constituting an emergency exist. Device sponsors should anticipate the likelihood of emergency use and obtain an approved IDE for such uses.

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 participating in the clinical investigation certify in writing the following:

- The subject is confronted by a life-threatening situation necessitating 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 the investigator believes that immediate use of the device is required to preserve the subject's life and time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the investigator should make the determination to use the device. Within five working days after the use of the device, the investigator should have the determination reviewed and evaluated in writing by a physician who is not participating in the investigation. The investigator must notify the Carilion IRB within five working days after the use of a test article using the IRB Single Patient Emergency Use Form in PRIS3M.

2. Compassionate Use: Individual (or Small Group) Patient Access to Investigational Devices Intended for Serious Diseases

The FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious condition and uses its regulatory discretion in determining whether such use of an investigational device should occur. Prior FDA approval is needed before compassionate use occurs. Compassionate use can be for devices that are being studied in a clinical trial under an IDE 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 or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation (such as an IDE for the device does not exist). This provision is typically approved for individual patients but may be approved to treat a small group. The sponsor must submit an IDE supplement requesting approval for a protocol deviation to treat the patient. The initial review of a Compassionate Use is to be completed by the convened IRB. Completion of an IRB Expanded Access or Compassionate Use Form is required in PRIS3M.

- The patient has a life-threatening or serious disease or condition;
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and
- Potential patient benefit justifies the potential risks of the investigational device.

3. Treatment Use of Investigational Devices

To facilitate the availability of new therapeutic and diagnostic devices to desperately ill patients, the FDA has established procedures to allow for the treatment use of investigational devices to patients with serious or immediately life-threatening diseases or conditions for which no comparable or satisfactory alternative device or other therapy exists. See 21 CFR 812.36 for more information. Treatment use of an investigational device will be considered when:

- 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 available to treat or diagnose 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 all clinical trials have been completed; and
- The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence

The sponsor should submit a request for treatment use as a supplement to the existing IDE to the FDA for approval in accordance with 21 CFR 812.36. Treatment IDEs may begin 30 days after the FDA receives the application, unless the FDA notifies the sponsor earlier than 30 days that the treatment use may or may not begin. The FDA may approve the treatment use as proposed, approve it with modifications/conditions, or disapprove it.

The FDA has safeguards in the treatment process that include:

- The distribution of the device through qualified experts
- Maintenance of adequate manufacturing facilities
- The submission of reports pursuant to 21 CFR 812.5
- Compliance with the regulations governing informed consent and IRBs

Prior IRB review and approval is needed. Investigators should submit the sponsor's supplement to the IDE requesting treatment use and submit the IRB Single Patient Emergency Use Form in PRIS3M.

4. Continued Access to Investigational Devices

Under the Continued Access Policy, the sponsor of a clinical investigation is permitted to continue enrolling subjects while a marketing application is being prepared 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. This process, known as extended investigation, may be applied to any clinical investigation that meets the criteria identified above. It is intended to be applied late in the device development process, after the controlled clinical trial has been completed. The sponsor's request for an extended investigation should be submitted as an IDE supplement. Prior IRB review and approval is needed. Investigators should submit the sponsor's supplement to the IDE requesting treatment use and a Carilion Clinic IRB application. If the trial has been reviewed and approved by an external IRB, treatment use can be sought from that IRB.