Clinical Research PATHWAYS

Opening Access. Advancing Treatments.

Intermediate-size Patient Population Expanded Access Use

A Flexible Alternative to Multiple Single Patient Uses

The intermediate-size patient population expanded access use should be considered when there is an expectation that there will be multiple single patient uses. This pathway may be used when a product is in ongoing development or when a product is not under active development. Obtaining a new intermediate-size patient population IND or modifying an existing IND minimizes the burden on physicians, product manufacturers, IRBs, and FDA while getting the investigational product to desperately ill patients more quickly.

Despite these advantages, intermediate-size patient population expanded access is underutilized. FDA reports that it received 47 requests for intermediate-size patient population INDs in 2017, and 45 were allowed to proceed (approved). The same year, FDA received 1,151 requests for single patient INDs, and 1,242 were allowed to proceed.

This document is intended to raise awareness about the option to obtain an intermediate-size patient population IND when treating multiple patients. Below five basic questions are answered:

1. **How are requests for intermediate-size patient population INDs initiated?**

   A product manufacturer, a physician, an investigator, or a private entity, acting in the role of a sponsor, may submit a request for an intermediate-size patient population IND to FDA. In some cases, FDA notices that multiple single patient expanded access requests have been made and allowed to proceed, and will suggest to the product manufacturer, the physician, or investigator (that is, the individual who is acting in the role of the sponsor) to seek an intermediate-size use. In other cases, the product manufacturer receives multiple requests for single patient expanded access INDs from an individual physician and recommends to the physician to seek an intermediate-size patient population IND.

   In a health care setting, such as a hospital or an academic institution, where a physician or medical department (e.g., pediatrics or oncology) plans to treat multiple patients with an investigational product, the hospital or physician may make a request to FDA for an intermediate-size patient population IND. If a physician is working with other physicians within his or her institution or at other institutions, the physician may make a request to FDA for an intermediate-size patient population IND. In this circumstance, the physician makes the request to FDA as the sponsor, and other physicians join as sub-investigators.

   Simply, different types of individuals (or entities) may serve as the sponsor and request an intermediate-size patient population IND. Further, the suggestion to pursue such a request may come from FDA, the product manufacturer, the physician/investigator, or even another entity.

2. When might it be appropriate to initiate an intermediate-size patient population IND?

- In place of multiple single patient uses involving an investigational product that is not available because the product is not being developed for marketing purposes or cannot meet the conditions for approval.

- When use is likely or may be predicted by a number of patients with a shared indication who may benefit from access to the investigational product.

- Instead of multiple single patient uses involving an approved product that is not available because there is a shortage of the product, where an alternate, but unapproved supply might be available. This might be, for example, a foreign version produced in a facility not registered under the New Drug Application (NDA).

- For Risk Evaluation and Mitigation Strategy (REMS) situations where the REMS may restrict use of approved products outside the approved indication, though patients with other conditions might potentially benefit from access to the product.

- To provide broader access to a promising therapeutic product under the auspices of an advocacy organization, as long as a physician associated with the organization files the application and takes responsibility to ensure proper administration and monitoring. This is especially useful in circumstances where a therapeutic product may offer benefit to patients with rare disease who are unable to participate in clinical trials.

- To allow access to treatment with an approved drug or biologic or a related product that is not available through marketing channels because it is no longer marketed. This expanded access pathway may also be used in the case of a drug shortage if an unapproved source of the drug, such as a foreign manufacturer, is available, provided the drug and the patient meet the general criteria for expanded access as and the criteria specific to use in an intermediate-size patient population. The intermediate-size patient population IND is the appropriate pathway in this situation, even if the number of patients exceeds 100, since the treatment IND is applicable only for drugs or biologics being actively developed for marketing approval.

There could be other situations that could be appropriate for an intermediate-size patient population use; the most common are listed above.

3. When should a physician or other sponsor seek an intermediate-size patient population IND?

When a physician or product manufacturer anticipates that there will be at least several requests and there is basic safety information, an intermediate-size patient population IND application should be considered.

What is considered basic safety information will depend on the specific circumstances of the use. For example, there might be phase 2 or 3 data available, or in the case of children, there might be safety data from the use of the investigational products in adults. More confidence in the safety of the product is preferred because with an intermediate-size patient population IND, patients who are unknown at the time the IND is granted will be enrolled in the treatment use.

This contrasts with a single patient IND, where the decision to grant the expanded access use includes medical history details specific to an individual patient.

4. What is required to apply for an intermediate-size patient population IND?

The individual who takes on responsibility for the intermediate-size patient population IND submits a protocol following the instructions for Form 1571. This individual may be a product manufacturer, a physician, an investigator, or a private entity, such as a patient advocacy group. It's important to note that Form 1571 is intended as an application for a new IND, including commercial INDs. Not every field is applicable to expanded access use.

Similar to FDA Form 3926 used for the individual patient IND, information to be submitted includes the name and address of the sponsor, name of the product, intended indication, parameters for patient eligibility, a proposed treatment plan, the type of expanded access being requested (e.g., intermediate-size patient population), the investigator's brochure, information about the institution, and the chemistry, manufacturing, and controls (CMC) information pertaining to the investigational product.

Because only the manufacturer usually has the required CMC information, a letter of authorization (LOA) from the manufacturer should be included to provide relevant identifying information, such as the sponsor's relevant application (e.g., IND) number. This allows FDA to cross-reference the CMC data from the original IND. The company will provide the LOA when they agree to provide product for treatment use.

Like Form 3926, Form 1571 requires a certification that treatment will not begin until IRB review and approval is secured.

In addition to the Form 1571, a Form 1572 must be completed for each physician/investigator who will administer treatment under the intermediate-size expanded access IND. If a commercial sponsor is filing the IND, they will usually collect Form 1572 from each physician who signs up to administer the drug to patients outside the clinical trial under the IND, and submit them to FDA under the IND.

Simplified Instructions on how to fill out Forms 1571 and 1572 can be found at How to Complete Form FDA 1571 and Form FDA 1572. More specific directions for filling out Form 1571 are available at Instructions for Filling out Form FDA 1571.

Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period when an IND is submitted to FDA to allow safety review of the product data and details of the intended use. FDA will usually respond sooner than the full 30 days.

5. What should the IRB consider when it reviews a protocol for an intermediate-size patient population expanded access use?

A convened IRB must review and approve the protocol using the criteria described in 21 CFR 56.111. Recognizing that the purpose is a treatment use, the IRB should interpret the criteria appropriately and should:

- Consider whether the safety information is reasonable in relationship to the anticipated benefit from the proposed treatment plan.

- Ensure that risks are minimized to the extent possible in the proposed treatment plan.

- Receive documentation from FDA that includes the IND number and any comments about the treatment use.

- Receive documentation that FDA has made its determinations regarding safety and effectiveness and has given clearance for the use (evidenced by issuance of an IND number).

- Review the protocol and determine that it makes adequate provision for ensuring the safety of the patients, including adequate monitoring (timing and type of tests/exams, etc.) and appropriate plans for collecting and reporting the data.

- Approve an informed consent process that is appropriate to a treatment use and ensure that it will be documented. Given the compassionate nature of the request and FDA's involvement, consent documents should meet the requirements listed in 21 CFR 50.25, using plain language that is specifically aimed at "patients" who expect direct benefit, as opposed to "subjects" who may not expect benefit. If some or all patients are not able to give informed consent, procedures to obtain appropriate permissions should be approved by the IRB.

If you have questions about pathways to investigational drugs, biologics, or medical devices, or are looking for the latest information on FDA expanded access or right-to-try, contact Clinical Research Pathways at info@clinicalresearchpathways.org.