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Intermediate-size Patient Population Expanded Access Use

A Flexible Alternative to Multiple Single Patient Uses

There are three tiers of access based on the size of the group of patients who will gain access. The intermediate-size patient population expanded access use should be considered when there is an expectation that there will be multiple single patient uses. It 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. The FDA website (see excerpt below) explains the two paths to approval for an intermediate size use.

> ***Intermediate-size Patient Population Expanded Access IND:*** *Access to an investigational drug (including a biologic) for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol* under a new IND. *The investigational product may or may not be under development for marketing. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment may begin.*
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> ***Intermediate-size Patient Population Expanded Access Protocol:*** *Access to an investigational drug (including a biologic) for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol* to an existing IND by the sponsor of the existing IND. *The investigational product may or may not be under development for marketing. 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 IRB approval before treatment may begin.*

Intermediate-size patient population expanded access is under-utilized. According to FDA statistics, in 2016, there were 42 requests for intermediate-size patient population INDs with 38 allowed to proceed (approved), compared to 1,471 requests for single patient INDs with 1,466 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?

2. What types of uses might be considered as appropriate for an intermediate-size patient population IND?

3. When to seek an intermediate-size patient population IND?

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

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

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, drug manufacturer, the physician/investigator or even another entity.

2. **What types of uses might be considered as appropriate for an intermediate-size patient population IND?**

a. 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.

b. An intermediate-size patient population IND or protocol may also be appropriate 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.

c. 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).

d. 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.

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

3. When to seek an intermediate-size patient population IND?

When a physician or product manufacturer anticipates that there will be multiple (e.g., five or more) 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 are 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 that 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 FDA Form 1571. This individual may be a product manufacturer, a physician, an investigator or a private entity, such as a patient advocacy group. 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. It's important to note that the 1571 is intended as an application for a new IND, including commercial INDs. Not every field is applicable to expanded access use.

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 for the treatment use. The IRB should consider whether the safety information is reasonable in relationship to the anticipated benefit from the proposed treatment plan. And further, that risks are minimized to the extent possible in the proposed treatment plan. The IRB should receive documentation from FDA that includes the IND number and any comments about the treatment use. The IRB should 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). The IRB should 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.

The IRB should approve an informed consent process that is appropriate to a treatment use and 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.