Investigational Drugs Outside of Clinical Trials: Understanding Expanded Access and Right-to-Try

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Patients who have no known effective treatment options for their serious disease or condition face daunting challenges. Clinical trials can allow access to potentially effective products; however, trials are designed to systematically test investigational therapies. Most investigational products that begin the clinical trial process do not prove safe or effective, and are dropped from development prior to regulatory agency approval.[1] If investigational products are provided outside of a trial, there is no formal system to collect data related to adverse safety events, or whether the product had the desired therapeutic effect, as there would be in an organized trial. Even when people believe they may benefit from a new drug, many do not meet the eligibility criteria to qualify for a clinical trial.

Access to Investigational Therapies

The Food and Drug Administration (FDA) has a system, known as expanded access, to provide investigational drugs outside of clinical trials.[2] Critics of this program have said that it is cumbersome and discourages many patients and physicians from applying, although the FDA revised their procedures in 2015 to make the process more user-friendly.[3] To combat what critics see as the deficiencies of the FDA system, a number of legislative actions have been passed at both the federal and state level, including various state "right-to-try" laws and the 21st Century Cures Act,[4] which are intended to provide access to investigational drugs without needing to go through the FDA process.

As a society, we are struggling to find the balance between helping people with serious or life threatening diseases accessing potentially beneficial treatments as soon as possible and ensuring that there is sufficient evidence of the benefits of these potential treatments to outweigh their risks. This paper will discuss the complex issues around giving patients access to investigational drugs during the development process.

Expanded Access

The current expanded access regulations have been in place since 2009, following enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA). As part of FDAMA, Congress granted explicit authority to the FDA to allow expanded access to investigational treatments.[5] The FDA created a three-tiered system for expanded access to investigational drugs (see sidebar). Regardless of the size of the population to be treated, all expanded access uses must meet the following criteria:

1. ***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;***
2. ***The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and***
3. ***Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.[6]***

Three Tier Expanded Access Program

The expanded access program has three tiers:

- single patient expanded access;
- intermediate population treatment use; and
- widespread treatment use.

Intermediate and widespread treatment use expanded access differ from single patient treatment use in that they involve creating protocols for larger populations and are generally set up where there may not be any appropriate clinical trials. For example, the drug may have completed all clinical trials and there is sufficient evidence to suggest that the investigational drug would not expose subjects to unreasonable risk. In addition, for intermediate and widespread treatment use protocols, there has to be more evidence that the investigational drug will provide a therapeutic benefit and the risks to the patients are reasonable. Please see 21 C.F.R. § 312.315 and 21 C.F.R. § 312.320 for more information.

Additional restrictions apply, including access generally limited to a single course of therapy for a specified duration unless the FDA expressly authorizes multiple courses for chronic therapy.[7] In addition to the criteria above, the FDA may permit an individual patient expanded access request if:

1. The physician determines (and provides a rationale for supporting) that the probable risk to the person from the investigational drug is not greater than that from the disease or condition;
2. The FDA determines that the patient cannot obtain the drug through other clinical trials.[8]

Applications can come from either the manufacturer of the drug or a licensed physician.[9] The FDA cannot require that a manufacturer provide the investigational drug under expanded access; by the time they reach the FDA, requests have generally already been reviewed by the manufacturer who agrees that providing the investigational drug is appropriate and feasible in this situation. During 2016, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) received 1757 expanded access requests, with CDER approving 1544 (99.4%) of the 1554 requests it received, and CBER approving 196 (96.6%) of its 203 requests.[10]

Right-to-Try Laws

The underlying argument for right-to-try laws is that patients with a terminal illness should have the right to choose how much risk they will accept, and should not be blocked from getting access to new therapies even if little is known about them. Right-to-try laws have been enacted in 34 states (as of May 2017).[11] The content of most of the state laws is based on the template legislation developed by the Goldwater Institute, although they may vary by state.[12] Some of the common aspects of these laws are that a manufacturer is permitted to provide investigational drugs to patients who:

- ***Have an advanced illness, attested to by the patient's treating physician.***
- ***Have considered all other treatment options currently approved by the United States Food and Drug Administration.***
- ***Have received a recommendation from his or her physician for an investigational drug, biological product, or device.***
- ***Have given written, informed consent for the use of the investigational drug, biological product, or device.***
- ***Have documentation from his or her physician that he or she meets the requirements of this subdivision.[13]***

The template legislation defines an investigational drug as one that has "successfully completed phase 1 clinical trials, but has not yet been approved for general use," although this may also be modified in specific laws.[14] As in the expanded access regulations, a manufacturer is not required to provide the investigational drug. Health insurance companies are not required to pay for the investigational drug or the cost of the services to provide the investigational drug.[15] One major difference is that the right-to-try laws explicitly allow the manufacturer to charge the patient for the investigational drug without further approval.[16] In contrast, the expanded access regulations allow the manufacturer to charge for an investigational drug, but a "sponsor may recover only its direct costs associated with making the drug available to the patient."[17] Critics of right-to-try laws are concerned that, among other issues, the laws allow unscrupulous health care providers to offer, and charge large fees for, unproven and highly risky "therapies" to desperate patients.

Therefore, the practical difference between existing expanded access regulation and the right-to-try laws to actually provide access to investigational drugs for individual people appears small. As tracked by the New York University School of Medicine Working Group on Compassionate Use and Pre-Approval Access, there is no evidence that any patients have successfully accessed investigational drugs under the right-to-try state laws that were not available to them under the already-existing expanded access regulations, and sometimes through already-approved expanded access programs.[18] Although many health care and policy organizations have been hesitant to take a public stance, the American Society for Clinical Oncology (ASCO) released a statement on April 4, 2017, in which they stated that the organization did not support the advancement of right-to-try legislation.[19] ASCO stated that the legislation did not remove any barriers to access (since they still do not mandate that manufacturers provide drugs), while removing the independent review provided by FDA which could lead to unintended harms.

The Future? 21st Century Cures Act Impact on Expanded Access

The 21st Century Cures Act (the Act) was signed into law by President Obama on December 13, 2016. This act could have tremendous impact on the expanded access program as it requires drug manufacturers and distributors to publicly disclose their policies for

making investigational drugs available in the expanded access program.[20] Without this information, a request for expanded access could be made without knowing if it would be rejected, or what would be needed to secure the drug. That delay and effort could have been a deterrent to even consider that option. With this information, physicians and patients could much more efficiently discuss expanded access options.

The manufacturers and distributors are required to provide contact information, any specific procedures for the request, any criteria used to evaluate the request, possible time interval to make any decision or acknowledgment of the request, and any reference or link to existing expanded access programs that may be available.[21] As needed for their circumstances, sponsors and manufacturers can amend their policy at any time, for example, if the development or manufacture of the drug should change.[22] The benefit to patients and physicians is that having these policies readily available will make the process of getting access to investigational drugs more transparent, but as with existing requirements, there is no requirement that investigational products will be available through expanded access or to an individual patient.[23]

Conclusion

The continuing push for right-to-try laws at both the state and federal level will keep national attention on this important issue, and will likely result in more organizations taking a public position in this debate.

The 21st Century Cures Act requirement for transparent information about investigational drug expanded access policies should produce improved communications between physicians, patients, and manufacturers.

We have a societal investment in providing the best care to people, both for immediate need and long-term planning. These laws highlight that the best way to do this is still under debate. Implementation of these laws will need to balance letting the individual determine how much risk they are willing to accept to possibly save their life, and ensuring that the products provided to people have evidence to support that the benefits outweigh the risk.

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