REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

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Subject: Expanded Access to Investigational Therapies

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Referred to: Reference Committee on Amendments to Constitution and Bylaws (Peter H. Rheinstein, MD, JD, MS, Chair)

Policy D-460.967(2), "Study of the Current Uses and Ethical Implications of Expanded Access Programs," instructs our American Medical Association (AMA) to "study the ethics of expanded access programs, accelerated approval mechanisms, and payment reform models meant to increase access to investigational therapies, including access for infants and children." This report by the Council on Ethical and Judicial Affairs (CEJA) examines ethical issues in relation to expanded access and offers guidance for physicians.

ACCESS TO INVESTIGATIONAL THERAPY

For some patients who face serious life-threatening or life-limiting conditions there are few or no approved therapies. For others, existing therapies are unlikely or have failed to be effective. In such situations, patients and their physicians may turn to as yet unapproved treatments as a last hope.

From a societal perspective, participating in a clinical trial is the most desirable way for patients to obtain access to therapies still in development [1,2]. But from the perspective of individual patients, enrolling in a randomized trial cannot guarantee access to the treatment they seek; some will not meet inclusion criteria to be accepted as trial participants even if they are willing to take the chance of being randomized to a control arm rather than the investigational therapy; still others may be unable to participate for other reasons. The expanded access program of the US Food and Drug Administration (FDA) allows patients in such circumstances to seek access to treatment with an investigational therapy outside a clinical trial.

Expanded Access ("Compassionate Use")

"Expanded access" refers "the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient rather than to obtain the kind of information about the drug that is generally derived from clinical trials [3].

Following the thalidomide scandal of the late 1950s and early 1960s, in 1962 the US Congress mandated that the FDA validate the safety and effectiveness of new drugs based on substantial evidence collected from controlled clinical trials, which significantly lengthened the timelines for development of new drugs [4]. The FDA began allowing patients and physicians to petition for access to unapproved drugs [4], and in 1987 recognized "treatment IND [investigational new

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drug]" protocols in response to the HIV/AIDS crisis as dying AIDS patients sought access to the then-unapproved drug AZT [5].

With the push from advocacy groups such as ACT UP, the FDA agreed to allow pharmaceutical companies to offer access to other promising AIDS drugs through an "expanded access" (or "compassionate use") protocol; Alzheimer and cancer patients and their advocates soon followed with similar demands for access to unproven therapies [5]. In 2009, the FDA substantially revised federal regulations (at 21 CFR 312), creating three categories for access to investigational therapies: use by individual patients, use by intermediate-sized patient populations (tens to hundreds), and widespread use after a clinical trial has been successfully completed but prior to FDA approval of the therapy [4,6].

Before a patient can legally receive an investigational therapy outside of a clinical trial, the FDA must approve the expanded access application submitted by the physician who will oversee treatment (21 CFR312.305). To be granted, a request must demonstrate that the patient(s) for whom access is requested has a "serious or immediately life-threating" condition for which there is no satisfactory alternative therapy; that the potential benefit to the patient justifies the risk of the investigational therapy; and that the potential risks of the investigational therapy "are not unreasonable in the context of the disease or condition to be treated" (21 CFR 312.305). To protect the scientific integrity of clinical trials, it must also be shown that providing the investigational therapy "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" (21 CFR 312.305).

The regulations further set evidentiary thresholds for risk that are more stringent the greater number of patients involved and the less serious the condition. For single patient use, a physician need only conclude that the investigational therapy poses no greater risk than the disease itself (21 CFR 312.310), while for intermediate-size patient populations, there must be evidence that the drug is safe "at the dose and duration" proposed for expanded access use and that there is "at least preliminary clinical evidence of effectiveness" (or plausible pharmacologic effect) to make use under expanded access "a reasonable therapeutic option" for the intended patient population (21 CFR 312.315). Thus, patients who receive investigational therapies outside clinical trials don't have the same protections as do enrolled participants, such as monitoring by institutional review boards and data and safety monitoring boards, which can halt trials when significant concerns arise [7]. Because patients receiving investigational therapies under expanded access are not connected to a particular trial site, "the potential for rigorous safety monitoring is greatly reduced" [7].

Under the 2009 regulations, the treating physician must determine that the proposed use meets FDA criteria for expanded access and is also responsible for obtaining IRB approval for use of the investigational therapy for the patient, which can be particularly challenging for physicians outside academic medical centers [4]. Physicians who treat patients with investigational therapies under expanded access must comply with the responsibilities for investigators set out elsewhere in federal regulations governing clinical trials. In 2017, the FDA took steps to streamline the process of applying for expanded access, simplifying the single patient application form and modifying the requirement for IRB approval to allow review by a single member of the IRB rather than the fully convened board [8]. FDA has indicated that further simplification is being considered [8].

Sponsors are not required to provide investigational therapies for use under expanded access, and FDA has no authority to mandate that a drug be made available by an unwilling sponsor [7]. Sponsors decline to participate in expanded access for a variety of reasons, including limited supply of the investigational therapy, limited capacity to produce additional supplies, or the cost of

making the therapy available outside an ongoing clinical trial [1,4]. Sponsors who provide an investigational therapy under expanded access face additional administrative burdens—among other requirements, regulations mandate that they ensure that physicians are qualified to administer the therapy and submit investigational new drug safety reports for the expanded access use, including reporting adverse events (21 CFR 312.305).

One concern is that adverse events reported for expanded access use may in fact not be associated with the investigational therapy and could jeopardize development of it [1,9]. Patients who receive an investigational therapy outside clinical trials may have more advanced disease than trial participants, have other concurrent medical conditions, or be receiving other concurrent treatment, which can make it more difficult to determine the cause of an adverse event. Responding to this concern, the FDA recently clarified expectations for reporting negative effects, permitting sponsors to report only those events for which "there is evidence to suggest a causal relationship between the drug and the adverse event" [8].

Impact of Expanded Access

Applications for expanded access use for both drugs and biologics have grown steadily—from just under 1,100 in 2010 to more than 1,700 in 2016 (with a high total of 1,999 in 2014) [10]. Overall, the Center for Drug Evaluation and Research received nearly 11,000 applications between 2005 and 2014, of which 99.7% were approved [1]. The majority of requests were in "therapeutic areas where products were being developed to treat life-threatening illness with significant unmet medical need," such as hematologic and solid organ malignancies [1].

Less is known about whether requests for expanded access use are granted by sponsors or whether investigational therapies provided through expanded access have received FDA approval. A review of found 398 expanded access programs registered at ClinicalTrials.gov as of July 2016 [11]. Of the 210 unique experimental drugs for which data were reviewed, 76 percent had ultimately received approval. As the authors note, this suggests that "we cannot entirely eliminate safety and efficacy questions in expanded access and compassionate use" [11].

The Future of Expanded Access

Provisions of the 21st Century Cures Act enacted in December 2016 address the challenges patients and physicians face in obtaining information about investigational therapies that may be available through expanded access. The act requires manufacturers and distributors of investigational drugs intended to treat serious diseases to "make public and readily available" their policies for evaluating and responding to requests for expanded access use (Pub L 114-255). The act further requires that such policies include contact information for the manufacturer or distributor, procedures for making requests and general criteria used to evaluate requests for individual patients, and a link or other reference to clinical trial information about the investigational therapy. The act does not, however, require a manufacturer or distributor to guarantee access to an investigational therapy in development.

In addition to simplifying application forms for single patient use and procedures for IRB approval, in July 2017 FDA launched a new online Expanded Access Navigator in conjunction with the Reagan-Udall Foundation to assist patients and physicians in finding information about expanded access [8].

ETHICAL CHALLENGES IN EXPANDED ACCESS

Although ongoing efforts to simplify expanded access programs will likely enable more patients to receive treatment with investigational therapies, ethical concerns remain. Key among them are issues of informed consent and decision making, fairness in access to investigational therapies, and possible negative effects for the conduct of clinical trials.

Informed Consent

Informed consent to medical treatment is fundamental in both ethics and law. Patients have the right to receive information and to ask questions about recommended treatments so that they can make well-considered decisions about care (E-2.1.1). Treatment with an investigational therapy poses special challenges in this regard. Patients who face serious, life-threatening illnesses for which approved therapies have not been effective or for which there are no approved therapies may be particularly vulnerable to holding out false hope for investigational therapy [12]. Promoting truly informed decisions about whether to request expanded access is critical, but can be difficult, both because information about an investigational therapy is often incomplete or difficult to obtain, and because patients may be prone to misinterpreting what information is available.

In the early stages of development, relatively little may be known about an investigational therapy's efficacy or possible adverse effects [4,13]. Information about therapies still in development is often proprietary and thus not readily available, making it difficult for patients and physicians to assess whether the risk of disease outweighs the risk of the investigational therapy for purposes of requesting expanded access [4]. Moreover, terminally ill patients do not always evaluate risks and benefits objectively—they tend to overestimate likely benefit and underestimate the burdens of as yet unproven therapies [12,14]. They may be under a "therapeutic misconception" and fail to appreciate that the therapy has not been demonstrated to be effective [15], or be "unrealistically optimistic" and expect that their personal outcomes will be more positive than the outcomes of others in similar situations [14,16].

FDA acknowledges that patients who are candidates for expanded access use "are a particularly vulnerable population" and "should be afforded a rigorous informed consent process that effectively communicates the risks and potential benefits of any investigational therapy to be used for treatment use [sic] in a way that does not raise false expectations about a positive outcome from treatment and makes clear what is unknown about the drug" [6]. Expanded access regulations mandate that the treating physician ("investigator" in the language of the regulations) ensure that the consent requirements of the Common Rule are met (21 CFR 305(c)(4)), including informing the patient that the therapy is investigational and that there is uncertainty as to its safety and effectiveness [3].

FDA also mandates that the sponsor of an investigational therapy provide the treating physician "with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug)" (21 CRF 312.305(c)(5)) as a requirement for expanded access use. It is essential that the treating physician have as much information as possible about an investigational therapy to provide appropriate patient care. An investigator's brochure "provides insight to support the clinical management of the study subject" [17]—or, in the instant case, the patient receiving the investigational therapy under expanded access—by compiling both clinical and nonclinical information about the therapy.

Financial Barriers to Expanded Access

Issues of equity also arise with respect to expanded access programs. Sponsors may provide investigational therapies at no cost for expanded access use, but they are not required to do so. Current FDA regulations permit sponsors to recover direct costs of providing an investigational therapy for expanded access use (21 CFR 312.8(d)(1)) , either directly from patients or by billing third-party payers. For the most part, insurance plans do not reimburse the costs of therapies not yet approved for marketing [14,18]. Although most sponsors shoulder the cost burden, when they do not patients may be unable to afford to pay out of pocket, even when they have been approved for expanded access use. It has been argued that expanded access "favors the rich or well-connected" [4].

Effects on Clinical Trials/Implications for Public Health

Expanded access programs may also adversely affect the successful completion of clinical trials and marketing approval of clinical trials. Permitting patients to obtain not yet approved therapies by means of expanded access may delay enrollment in trials of the therapy or jeopardize retention of participants, undermining efforts to demonstrate the safety and efficacy of the investigational therapy [9]. This in turn thwarts society's interest in the development and approval of new therapies for populations of patients [2,9]. The extent to which expanded access programs in fact have this effect is not clear. Before FDA will approve a request for expanded access use, patients and physicians must demonstrate that the patient is not a candidate for a clinical trial, for example, because the individual fails to meet inclusion criteria or existing trials are geographically inaccessible to the individual.

RECOMMENDATION

In light of these considerations, the Council on Ethical and Judicial Affairs recommends that Policy D-460.967(2), "Study of the Current Uses and Ethical Implications of Expanded Access Programs," be rescinded, the following be adopted, and the remainder of the report be filed:

Physicians who care for patients with serious, life-threatening illness for whom standard therapies have failed, are unlikely to be effective, or do not exist should determine whether questions about access to investigational therapy through the U.S. Food and Drug Administration's "expanded access" program are likely to arise in their clinical practice. If so, physicians should familiarize themselves with the program to be better able to engage in shared decision making with patients.

When a patient requests expanded access to an investigational therapy, physicians should:

(a) Assess the patient's individual clinical situation to determine whether an investigational therapy would be appropriate, including:

(i) whether there is a satisfactory alternative therapy available to diagnose, monitor, or treat the patient's disease or condition;

(ii) the nature of potential risks of the investigational therapy and whether those risks are not unreasonable in the context of the patient's disease or condition;

(iii) whether the potential benefit to the patient justifies the risks of the investigational therapy;

(iv) whether the patient meets inclusion criteria for an existing clinical trial of the investigational therapy.

(b) As part of the informed consent process, advise the patient (or parent/guardian if the patient is a minor) that the investigational therapy has not yet been demonstrated to be effective in treating the patient's condition and may pose as yet unknown risks. Physicians should explain the importance of clinical trials, encourage patients who meet inclusion criteria to participate in an existing trial rather than seek access to investigational therapy through the FDA expanded access program, and direct patients who wish to participate in research to appropriate resources.

(c) Decline to support an application for expanded access to an investigational therapy when:

(i) the physician judges the treatment with the investigational therapy not to be in the patient's best interest, and explain why; or

(ii) the physician does not have appropriate resources and ability to safely supervise the patient's care under expanded access.

In such cases, physicians should refer the patient to another physician with whom to discuss possible application for expanded access.

(d) Discuss the implications of expanded access for the patient and family and help them form realistic expectations about what it will mean to be treated with the investigational therapy outside a clinical trial. Physicians should alert patients:

(i) to the possibility of financial or other responsibilities associated with receiving an investigational therapy through expanded access;

(ii) to the lack of infrastructure to systematically monitor and evaluate the effects of the investigational therapy outside a clinical trial;

(iii) that they need information about how to contact the manufacturer for guidance if they seek emergency care from a health care professional who is not affiliated with a clinical trial of the investigational therapy;

(iv) that the physician has a responsibility to collect and share clinical information about the patient's course of treatment with the investigational therapy, as well as to report any adverse events that may occur over the course of treatment;

(v) to the conditions under which the physician would recommend stopping treatment with the investigational therapy.

(NEW HOD/CEJA POLICY)

Fiscal Note: Less than $500

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