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The Critical Role of Medical Institutions in Expanding Access to Investigational Interventions

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Exhausting standard-of-care treatments for a life-threatening condition frightens patients and clinicians alike. It is one of the most difficult dilemmas faced at the bedside. In these complex situations, clinicians can either transition to care focused on keeping the patient comfortable or attempt to enroll the patient in a clinical trial of an investigational approach. In many cases, however, there is no relevant trial. And if there is a trial for the patient's condition, the patient is often not able to enroll because of comorbid conditions or logistical or financial hurdles.

This situation sometimes leads patients and their clinicians to seek the hybrid option of "expanded access" to interventions currently under study for potential clinical benefits. Yet an inherent tension exists: clinicians have a fiduciary duty to take individually tailored care of patients, but the overarching goal of investigational trials is not to take care of patients or prolong their lives. It is to produce data about what will and will not likely work in taking care of *future* patients. While advocates of expanded access often frame this decision as one for patients otherwise "running out of other options," using an expanded access pathway can preclude a timely transition to palliative care.[1] Thus the space in which expanded access exists—neither fully clinical care nor originally a clinical trial—should never be framed as a no-cost endeavor; potential burdens to patients, clinicians, and the community require a thoughtful and coordinated approach.

U.S. federal courts have declined to recognize a constitutional right for patients to have such expanded access,[2] but in response to these extremely compelling circumstances, the federal government provides two tracks to obtain investigational options outside of clinical trials: the Food and Drug Administration's expanded access pathway and the pathway created by the more recent Right to Try Act.[3] These two options have been well debated in the literature,[4] and in this issue of the *Hastings Center Report*, Kelly Folkers and colleagues clearly and thoughtfully articulate the ethical and regulatory landscape of expanded access and right to try.[5] With a critical focus on patients, industry, and the research enterprise, Folkers and colleagues frame the inherent challenges that expanded access and right to try are meant to solve and have also inadvertently created. But an additional key perspective is how these situations should be managed at the bedside and how the system risks both inefficient and inequitable access to options at the institutional level. Although either pathway could be helpful to patients, the challenges of having expanded access and right to try exist concurrently are greater than the sum of their parts. Individual clinicians represent the front line of the regulatory and eligibility challenges of expanded access and right to try, making clinical education a critical component of a comprehensive approach to using them

well. But it is medical institutions that must take the lead on supporting access to investigational options in the most equitable and effective manner possible for all patients.

Since the 1980s, the FDA's expanded access pathway has given patients a formal channel through which to request investigational drugs, biologics, and devices if they have a serious or immediately life-threatening disease or condition with no comparable alternative. The FDA can make suggestions to clinicians about dosing regimen and side effects as well as other therapies that may be more helpful (information that may otherwise be unavailable to treating physicians).[6] Both the FDA and an institutional review board must authorize the request. The physician overseeing treatment must submit an FDA authorization application for the expanded access case and maintain basic safety reporting and record keeping. The FDA receives over one thousand such requests per year, reviews them within hours or days, and approves over 99 percent.[7]

The federal Right to Try Act, signed in 2018, facilitates the request by an eligible patient and then physician for access to an eligible investigational drug (but not device) if the patient has a life-threatening disease and has exhausted other treatment or trial options. Forty-one states have their own right-to-try legislation, and several more have legislation pending.[8] Possibly in response to the new right-to-try pathway, the FDA recently proposed a new Project Facilitate, to be piloted in 2019, to further simplify and improve the expanded access pathway. Under this rubric, both patients and providers may contact the FDA through a streamlined authorization process, and if the manufacturer declines to provide the drug, the FDA will request a reason for the decision in hopes of encouraging access.[9] But several clinician-level and institutional-facing problems remain.

The existence of the tandem pathways generates several challenges. First, both approaches require a prescribing clinician, which means the initial critical decisions start at the bedside. Key questions include whether the clinician should suggest one of the pathways as a possible option for the patient and, if so, which one? If the patient asks to use a specific pathway, can a clinician ethically decline one or the other based on personal practice preferences? Having a solid working knowledge of expanded access options, whether and how to use expanded access or right to try, and the logistical procedure to make that happen, requires guidance, time, and effort—a combination rare at the individual clinician level.

Second, the quagmire of the dual pathways might actually enable disparities in access. Both of them protect the right for a clinician or her patient to take formal steps to request access to an investigational option; neither compels the manufacturer to provide it. Many of the well-known cases of patients gaining access to drugs in this way have required polished social media and lobbying campaigns. Such actions require not only that families or their physicians know that such laws exist but also that they have sophisticated social networks—and media interested in covering the story—to exert pressure on the company.

For example, in 2014, the parents of Josh Hardy launched an exuberant campaign to pressure Chimerix, Inc., to provide them with access to brincidofovir. Hundreds of patients had already pleaded with Chimerix for use, but with this immense social pressure, Josh became the first to gain it.[10] (Folkers and colleagues also discuss this phenomenon.[11])

However, pressure could in theory also come from the clinician: structurally, what is to prevent a clinician (either consciously or unconsciously) from advocating in this way for only some of her patients? Also, if some clinicians are willing to write a prescription only under the expanded access pathway or only under the right-to-try pathway—or neither—then they may be treating their own patient population equally, but they might create a bias at the institutional level (particularly if certain clinicians are more likely to see one specific community of patients, such as those that are privately insured versus those on Medicaid or those who have access to social support resources). Thus, while the Hardy case is a good example of the power of individual patients or families to propel legislative change, health systems that empower individual patients and their families instead of providing systemic public health-focused approaches leave room for bias at both the clinician and institutional level.

Unfortunately, right to try aggravates such inequities by taking a key element of control out of the hands of the institution: IRB review. Both pathways still require some involvement by the FDA. A manufacturer's distribution of an unauthorized drug directly to a patient without an active Investigational New Drug Application is still a violation of the federal Food, Drug and Cosmetic Act. The premise of the FDA's investigational exemption paths is to test whether the intervention will be safe and effective for future patients. Research participants, even those who are also desperate patients, are not intended to be the key beneficiaries. In order to help clinicians balance and communicate these potential risks and benefits with their patients, the expanded access pathway requires institutional involvement via IRB authorization. Right to try does not (although it does not prohibit it). Without mandated IRB oversight, and particularly if patients are unequally receiving access at institutions via an IRB-approved pathway, institutions have little control over either clinician confusion or institutional-level inequities in access.

This lack of IRB oversight in right to try creates a fourth problem: inadequate protections for potential participants due to shortcomings in informed consent oversight. The clinical informed consent process is focused on the risks, benefits, and alternatives of health interventions for a single patient. Sometimes, great physiological risks are acceptable due to the inherent proportionality of trade-offs in the setting of life-threatening illness. Yet, at other times, minor physiological risks are unacceptable to a patient due to other quality-of-life considerations. But the clinical risk-benefit analysis is tailored to the individual.[12] In research, the underlying premise of equipoise generally compels us to render this balance differently: benefits may not redound to any individual patient, and we must weigh risks we expect research participants to accept at the cohort level. The processes of informed consent to clinical care and of informed consent to clinical research thus have fundamentally different goals. IRBs are experienced and adept at framing this delicate balance for individual protocols.[13] But without mandatory IRB oversight of the right-to-try pathway, it is unclear whether in the clinical setting individual clinicians are providing the information necessary for their patients to give fully informed consent to an investigational intervention (although some state right-to-try laws may offer additional protections). Compounded by the vulnerability of patients with serious life-threatening diseases, the potential for coercion or incomplete patient comprehension is high.

Last, expenses absorbed by patients and institutions can generate a challenge for clinicians (distinct from that posed by the societal costs[14]). Practically, if institutions are not taking responsibility for the oversight, logistical, and health care system issues of expanded access or right to try, then they are not going to be reimbursed for either administration of the intervention or the associated medical treatment. If these costs are billed to patients (particularly patients who are dying, are already facing large medical bills, or were treated before the insurer had time to assess coverage), then the hospitals are less likely to recover costs associated with the pathway (although pharmaceutical companies that elect to charge for investigational access are unlikely to provide access before being reimbursed, potentially providing an inadvertent backstop to a groundswell of requests). Physicians and institutions are often on the front line of interactions with insurers to obtain coverage for specific drugs and treatments, and hospital administrators are incentivized to control these negotiations and outcomes at the institutional level—rather than clinician by clinician—to protect vulnerable patients.

Because federal right to try is new, the risks and benefits of expanded access as compared to right to try and as compared to their existence in tandem are still largely theoretical. Folkers and colleagues emphasize how these barriers will require FDA clarification in the future—but health care providers and their institutions must respond to the current state of affairs starting immediately. Institution-level reconciliation of IRB policies, administrative burdens, and interactions with companies cannot be solved by the federal government. For example, establishing an agreement with the company providing the investigational agent is a prerequisite for both expanded access and right to try and requires immense coordination at the institutional level. Corey Frederick et al. recently published a case study on the difficulty of using the expanded access pathway in an extremely time-sensitive situation to obtain fosfomycin for a patient with an infectious disease resistant to standard treatments.[15] They make concrete suggestions for how institutions can be ready for such cases, including identifying in advance which personnel to involve and what steps will be necessary, estimating costs and length of therapy, and being cognizant of how long it will take to procure the drug. Needless to say, the coordination necessary at the institutional level to succeed in these cases is critical, and the steps that must be taken are poorly understood.

The potential conflation of clinical care and research is complex enough—let alone in a politically charged circumstance combining passionate practitioners, vulnerable patients, and potential systemic bias. Additional empirical research is needed to fully understand the patient's and clinician's perspectives as well as the logistics, economics, and impact of these programs. With that data in hand, we could formulate best-practice recommendations to move forward,[16] and, therefore, we have research under way on institutions' current practices.[17] But, in the meantime, there are several ways in which institutions can immediately begin improving their processes.

Medical centers must reinforce to their clinicians that the expanded access and right-to-try pathways remain avenues of last resort. Offering access to investigational options outside of the protective protocol of a research trial can be dangerous, particularly if the options are still in phase I or II trials and have not been established as safe or effective. FDA-authorized therapeutics or existing trials are preferable. Institutions must also take a leadership role in

ensuring that clinicians understand the appropriate use of expanded access and right to try, supporting patients seeking research opportunities, and providing a cohesive plan to encourage traditional avenues. Institutions need clear policies for how the pathways can and will be used and overseen to fill the chasms that competing regulatory structures have created and to provide the critical support for clinicians dealing with vulnerable patients on the front line.

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