Informed Consent in Right-To-Try Cases

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There has been a surge since 2014 in state legislation addressing the topic of access to investigational treatments for persons who are terminally ill and have exhausted standard medical management. These laws, commonly called "right-to-try" laws (a play on "right to die"), are intended to provide patients with timely access to investigational medical treatments without the approval of the U.S. Food and Drug Administration (FDA) and institutional review boards (IRBs). Investigational treatments, also called experimental treatments, are medical treatments in the process of being studied to determine safety and efficacy; they have not received approval from the FDA for public use.

In the United States, medications are generally not available to the public until they have gone through a series of clinical trials and received approval from the FDA. The FDA has three phases of clinical trials. The focus of phase I is to monitor basic patient safety information, not treatment efficacy.[1,2] The focus of phase II remains on safety, but the study involves a larger sample of study participants. Phase III focuses on both safety and efficacy of treatment. Although there are some exceptions to this process through the FDA's accelerated access programs, it typically takes several years for a drug to become available to those who seek it. Further, only a fraction of drugs make it through the FDA process. A 2014 study demonstrated that approximately 1 in 10 drugs makes it through the FDA process and is approved for clinical use.[3]

When approved treatments fail to remedy patients' conditions, some patients with serious or terminal illness seek to try investigational treatments. The standard procedure is for patients to try investigational agents through clinical drug trials, during which efficacy and adverse events are monitored. However, some patients are not eligible or willing to participate in clinical trials. Clinical research trials commonly require specific eligibility criteria that may preclude certain patients from participation. Sometimes, the site locations for the clinical trials are too far away from a patient's home for the patient to participate. Further, some patients do not want to risk being assigned to a control group of the clinical trial where they would not obtain the experimental treatment.

Under the FDA regulations, patients may alternatively apply for expanded access or emergency use of an experimental treatment. These expanded-access programs, sometimes referred to as "compassionate use," enable patients with life-threatening illnesses to appeal for use of investigational treatments outside of a clinical trial and before the drug has been approved for public use by the FDA. These require approval by the FDA and by the IRB at the institution where the drug will be dispensed. The right-to-try movement aims to make it even easier to gain access to investigational treatments.

Although the specifics of the laws differ by jurisdiction, the state right-to-try laws largely are meant to streamline access to certain investigational treatments by bypassing the requirements of FDA and

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IRB approval. Proponents of right-to-try laws argue that it places an undue burden on sick patients to require approval from the FDA and IRBs. In general, these laws allow physicians and pharmaceutical companies to provide drugs, biologics, or other medical devices to certain patients (typically, terminally ill) once the treatments have passed phase I of the FDA's clinical regulatory testing scheme.

In addition, the right-to-try laws aim to encourage industry participation by limiting or absolving physicians and/or drug manufacturers from legal liability for those who prescribe or manufacture the investigational treatments. Although the laws vary by jurisdiction, the Louisiana law is illustrative, in that it provides physicians with immunity to tort liability for prescribing investigational treatments to those eligible under the state law[4]; Colorado, for example, provides some civil liability protection to both clinicians and drug manufacturers.[5]

Historical Perspectives

In 1938, with modification of the Pure Food and Drug Act,[6] the federal government began requiring a formal safety review before marketing a new drug. Initially, the law did not specify the testing requirements, but the Act provided some authority for the FDA to require manufacturers to submit additional data or risk the halt of their marketing efforts. The 1962 Drug Amendments provided clarification for testing, requiring both safety and efficacy for drug approval.[7] Although it has been credited for advancing the roles of drug efficacy and accuracy in marketing, critics note that the number of new drugs introduced in the 1960s fell substantially compared with the 1950s.[8]

The FDA in 1962 started an informal process to approve access to investigational drugs on a case-by-case basis. The process called for physicians to contact the FDA to request access for patients with severe illness that had no other options but to try an experimental treatment.[9] Although this allowed sick individuals to request access with a minimal burden of paperwork, the informal approach led to confusion and favored patients whose physicians were familiar with drugs under investigation. There was limited review for the appropriateness of the physicians' requests.[9]

Starting in the 1980s, in part as a reaction to the need to treat persons with HIV/AIDS, the FDA approved several discrete programs aimed at expanding access to drugs for persons with serious or life-threatening illnesses. The programs focused on two categories: groups of persons with the same disease and individual requests. Individuals applying for emergency use must obtain approval by the manufacturer of the investigational treatment, submit an application to the FDA, and obtain approval from the IRB of the institution where the treatment will be provided. The FDA determines whether the potential benefits of expanded access justify the potential harms. It also considers whether approval of a drug via expanded access would compromise a clinical trial.

In 2009, the FDA updated its criteria for expedited access to investigational treatments and authorized use of drugs before completion of phase I trials in some circumstances.[10] In 2015, the FDA announced changes to make the application process easier to request approval.[11] The goal was to reduce the time it takes to complete requests for expanded access or experimental use of investigational treatments. The FDA has approved 99 percent of the expanded access requests.[12] Despite these changes, advocates for right-to-try laws urge additional measures that will increase access to investigational products.

Seeking a Constitutional Basis for Right-to-Try

Although there has been a surge in right-to-try laws in the past couple of years, this idea is not new, nor is the idea of challenging the FDA to ease access to investigational drugs. One of the first serious legal challenges to the FDA's authority was *United States v. Rutherford* (1979).[13] In *Rutherford*, terminally ill patients sued to gain access to a cancer treatment that had not been approved in the Unites States, but was available in other countries. The U.S. Supreme Court addressed whether there should be exceptions to the FDA's safety and effectiveness requirements to ease access to drugs for terminally ill patients. The Court held that the 1962 Drug Amendments required that no drugs be distributed to patients without sufficient safety and effectiveness testing. It stated that there is a rational relationship between the terms "safety" and "effectiveness" and legitimate government policy. The Act's legislative history revealed that Congress had specifically identified terminally ill patients as a class needing protection from possible

mistreatment. Other courts have ruled that there is no fundamental right to specific treatments.[14]

Following on the heels of right-to-die legal challenges, the Abigail Alliance for Better Access to Developmental Drugs (an advocacy organization) filed suit alleging that the FDA's policies violated terminally ill patients' due process in relation to right to life. The suit was based on Abigail Burrough's failed efforts to gain access to investigational treatments for her cancer. In *Abigail Alliance v. von Eschenbach* (2007),[15] the D.C. Circuit Court of Appeals considered whether terminally ill patients have a due process right to access drugs that have passed limited safety trials (phase I) but have not been proven safe or effective. The Court relied on the two-pronged due process analysis articulated in *Washington v. Glucksberg* (1997) (holding that a state's prohibition against aiding suicide does not violate the due process clause): whether the fundamental right is deeply rooted in the nation's history and whether the asserted liberty interest is carefully described.[16] The *Abigail* court intimated that, since the FDA regulated safety as well as efficacy in post-phase I trials, the regulations were consistent with this historical tradition. The court held that there was no fundamental right for terminally ill patients to access post-phase I investigational new drugs.

State Right-to-Try Movement

Although there are avenues for pursuing use of experimental treatments through the FDA's expanded access policies, advocates for easier and earlier access to these resources turned to the states. The Goldwater Institute (an advocacy organization) was instrumental in leading and creating model legislation to advance this cause. In 2014, the institute issued a policy report on the topic, advancing the argument that there is a fundamental right for terminally ill patients to access investigational drugs that have gone through basic safety tests.[17] The policy report includes the organization's position about the procedural burdens of requiring FDA and IRB approval for investigational drugs. The policy report also outlines the requirements of informed consent, a physician recommendation for the experimental treatment, and manufacturer participation in supplying the treatment.

In 2014, five states passed right-to-try laws modeled after the Goldwater legislation[18]: Colorado, Louisiana, Michigan, Missouri, and Arizona. In addition, some states, such as Utah, adopted legislation to study terminally ill patients' access to investigational drugs.[19] Since 2014, right-to-try laws have become law in more than 20 states, and additional legislation has been introduced in several states.[12,18] The Regulatory Affairs Professionals Society maintains an updated list of states with recently enacted and proposed right-to-try legislation.[12] Governor Jerry Brown made headlines as the first governor to put the brakes on the momentum of right-to-try advocates; he vetoed California's recent legislation on the topic in October 2015.[20]

Some scholars have asserted that state right-to-try laws are essentially moot.[21] This is because, in general, federal regulations pre-empt conflicting state laws. To date, however, the federal government has not challenged the state right-to-try laws as being in conflict with federal law. Should this occur, the state laws are at risk of being invalidated according to the Supremacy Clause of the United States Constitution.[22] On the other hand, proponents of these laws invoke the notion of federalism and the role of state governments in protecting their citizens from excessive control from the federal government.[23] There is some support for this in looking at other circumstances where the United States Supreme Court has narrowly construed federal statute to avoid conflict with state law. For example, returning to the right-to-die movement, the Supreme Court in *Gonzales v. Oregon* (2006) narrowly construed the federal government's ability to regulate prescriptions under the Controlled Substance Act such that it did not nullify Oregon's physician-assisted dying law.[24] Oregon's Death with Dignity Act remains in effect.

Whether state laws are challenged by federal preemption or not, the fact that so many states have enacted right-to-try laws and that the public has demonstrated such support for increasing access to investigational agents may nevertheless influence future lawmakers and bring about further changes to federal law. In fact, in July 2015, three members of the U.S. Congress introduced a bill aimed at preventing the federal government from overriding state right-to-try laws.[25] This effort and some other recent attempts at new federal legislation have not made it out of congressional committee. It is prudent to understand these laws and consider what procedures should be in place to protect patients seeking easier access to investigational treatments.

Key Arguments and Ethics Considerations in Right-to-Try Laws

On an individual level, patient autonomy is central to the right-to-try movement. Advocates in support of right-to-try laws argue that patients should have a right to life and a right to choose an agent that might prolong their lives. They argue that patients should not be resigned to waiting for death once they have exhausted standard treatments because they, by choice or eligibility restrictions, are not participating in a clinical research trial.

In support of this opinion, proponents of these laws assert that applications through the FDA's expanded-access program remain time consuming and burdensome for patients and clinicians. This logic dictates that terminally ill individuals should not be burdened with FDA and IRB hurdles when their life expectancy is limited. A study before the 2015 FDA expanded access-approval modifications revealed that it took approximately eight hours to complete the FDA expanded access application.[26] This does not include the time it takes to identify and research possible experimental agents and communications between patients and their treatment clinicians in making decisions to purse these experimental options. Further, only a fraction of studies listed on ClinicalTrials.gov, a registry of clinical trials, list eligibility for expanded access.

On the other hand, opponents of right-to-try laws raise concerns that they minimize the potential serious risks that come with taking investigational medications. Under these laws, patients may seek investigational drugs that have only completed phase I FDA clinical trials, which means that patients may seek and obtain medications that have not been tested for efficacy. Many drugs that complete phase I trials fail to receive FDA approval because, in later trials, they are found to have serious side effects or are ineffective. Given this possibility, the odds are low that a patient would have significant therapeutic benefit from an agent obtained under a right-to-try law. In contrast, these agents could have serious side effects or hasten death. By seeking investigational treatments, patients could be forgoing end-of-life measures that would improve their remaining quality of life.

The right-to-try laws also raise questions as to an equitable balance between individual and societal interests. Under state right-to-try laws, patients may seek access to investigational treatment directly from manufacturers. The manufacturers are under no obligation to supply the medication. Some manufacturers may decline requests; some may give the drug to patients who seek it; and others may charge the patient potentially hefty sums for the investigational treatment. Under some right-to-try laws, patients have to waive use of their regular medical insurance for managing any side effects or medical complications associated with their use of the investigational treatment. Patients may be personally financially responsible for paying for care that is related to their use of the investigational agent. Those with financial means are therefore likely to be the ones with greater access to these treatments.

In recent years, some patients have turned to online petitions to gain access to investigational drugs.[27] It is foreseeable that patients will continue to use these online venues to garner public support in an effort to persuade or pressure manufacturers into providing the requested investigational drug, raising the question of fair allocation of sparse investigational resources. For example, public campaigns and manufacturers may be influenced to make available drugs that would be given to a young child, but they are less likely to make the same agent available to an elderly person, particularly if the adult was perceived as contributing to his illness (e.g., not attentive to health care when he had the chance or used illicit drugs). At least one company, Janssen, has sought independent assistance for a fair method to review compassionate-use requests under the FDA's expanded access and emergency provisions.[28] At this point, manufacturers are under no obligation to develop criteria that they would use to determine which patients should have access to its investigational agents.

Granting requests from individuals for investigational treatments may compromise the development of the treatments that would ultimately benefit a larger number of people. Patients who obtain investigational treatments through right-to-try laws bypass the FDA and the regular clinical trials. When drugs are available without going through clinical trials, it can compromise the ability of a manufacturer to recruit and conduct clinical trials. This hindrance has consequences because the clinical trial system is necessary to determine drug effectiveness. It takes longer to determine a drug's efficacy in clinical trials, delaying some drugs that would be FDA-

approved from reaching patients. In addition, an adverse event in the context of a right-to-try case may have an unintended impact on further clinical trials. Should news of the adverse event become known, fewer people may enlist in the clinical trial and negative attention may have financial ramifications for the manufacturer that could limit further development. In this manner, opponents to right-to-try laws argue that an individual's request should not trump the public's access through the FDA approval system.

Informed Consent

Voluntary informed consent is a hallmark of clinical and research practice. Proponents of the state right-to-try laws point to patients' presumption of capacity to make informed medical decisions. Consistent with the rationale for the laws, they assert that patients should be able to weigh the risks based on communications with their physicians and their own values. The patients, in conjunction with their medical providers, should determine whether the benefits of seeking an investigational treatment outweigh the risks.

However, others question whether true informed consent can be given in this context. Because the investigational treatments sought may be in early stages of FDA approval, there may be little information available about the benefits and risks of the agent. Absent such data, it is difficult for physicians to weigh the risks and advise their patients; similarly, it is unclear how patients will make use of such limited data to make informed decisions. Previous studies have demonstrated that patients have high, and perhaps unrealistic, expectations of therapeutic benefit when enrolling in clinical trials[29–31]; the risk of therapeutic misconception is likely to be true with patients seeking investigational treatments under right-to-try laws.

In some respects, informed consent under right-to-try laws is analogous to that in the research setting. For a consent to be ethical and valid, the patient must be free to make a voluntary decision in the absence of coercion or undue influence. In addition to challenges associated with providing patients with sufficient information about the investigational treatment, patients may be subject to the influences of their family members, physicians, and drug manufacturers, who may have their own motives for encouraging the patient to seek investigational measures. In an interview study of patients enrolling in cancer treatment trials, Sulmsay and colleagues[30] reported that more than a third of participants attributed their optimism about the trial to the expectations of others. They sought to be "model patients" or please their family.

Likewise, there are potential conflicts of interests for the treating doctor when he or she also participates in the administration of an investigational treatment because the physician may have personal motives to try the investigational agent. Similar to ethics-related risks in research trials, the physician's obligation to treat the patient in a way that is most beneficial to the patient may not be consistent with research motives or procedures for evaluating the investigational drug. In some cases, influence from others may compromise a patient's ability to consent voluntarily to the treatment. Accordingly, it could be argued that these patients require more protection by the FDA and other regulators of access to these drugs.

Similar to the research setting, informed consent requires adequate disclosure of information to the patient about the risks and benefits of participation. As discussed above, there are complex ethics and practical considerations that a patient should be familiar with before making a decision to obtain right-to-try treatments. At the phase I investigational stage, little is known about the treatments. There is no guarantee that the treatments will be effective, or even safe. In the setting of right-to-try laws, however, additional information about the process and potential risks should be disclosed to patients. Patients should be informed of possible financial considerations. They may be required to purchase the drug as well as pay for management of any medical conditions associated with use of the drug. Patients should also be informed of how their use of investigational drugs outside of clinical trials may compromise the development of the treatment for a larger number of patients in the future. They may have mistaken beliefs about their role in helping future generations.

Patients seeking right-to-try treatments should also possess decision-making capacity. Certainly, patients with serious or terminal illnesses may have co-occurring mental illness or otherwise have conditions that affect their ability to understand and appreciate the consequences of their health decisions. Obtaining information is one thing. These patients must also be able to understand the basic factual information about the investigational agent and process of right-to-try laws, appreciate their situation, ratio-

nally manipulate the information, and communicate or give evidence for their choice.[32]

Call for Secondary Review of Informed Consent

Like other vulnerable populations, such as prisoners and other institutionalized personnel, patients seeking access to right-to-try treatments face barriers to voluntary informed consent in some circumstances. In the landmark case of *Kaimowitz v. Department of Mental Health for the State of Michigan* (1973),[33] the Michigan Circuit articulated the rationale for scrutinizing the informed consent for vulnerable persons. In *Kaimowitz*, a patient committed to a state psychiatric institute, consented to experimental brain surgery to control aggression. In reviewing the consent process, the court raised concerns about the substantial risks to the patient. In *Kaimowitz*, the court held that the patient, by nature of being in a "total institution," could not give truly voluntary informed consent to the experimental procedure. Although patients seeking right-to-try treatments are not confined by an institution, they are confined by the terminal state of their illness and may be considered vulnerable. The *Kaimowitz* court emphasized that close scrutiny should be given to the adequacy of one's informed consent when an experiment is risky and of uncertain benefit to the patient.

In contrast to the traditional research setting, the right-to-try laws remove certain protections afforded patients because they bypass the requirements of FDA and IRB approval. The FDA and IRBs, even in the setting of expanded access and emergent use of investigational drugs, serve as secondary reviewers of the procedure for informed consent. Given the complexity and opportunities for conflicts of interest and undue influence, something similar should be available for right-to-try seekers. The approval could take the form of review by IRBs, ethics committees, a procedure for an independent second opinion by a neutral evaluator who is not involved in the care of the patient or the investigational agent, an ombudsman program, or the development of a national consent review board for investigational agents, among other options. Many institutions have emergent IRB procedures for cases in which the IRB must review and render decisions about specific cases in an expeditious manner. Similarly, many institutions have avenues for on-call ethics consultation. "Nothing in the history of [FDA legislation] suggests that Congress intended protections only for persons suffering from curable diseases."[13]

Although it may be appropriate for psychiatrists to be cautious about serving in the roll of a gatekeeper for persons seeking access to investigational treatments under right-to-try laws, they have a unique set of skills and experiences that could aid physicians requesting investigational agents for their patients, agencies, legislatures, and institutions considering ways to afford improved protections for persons pursuing investigational agents under right-to-try laws. Psychiatrists commonly perform assessments of persons' capacity for medical decision-making, have general familiarity with the FDA drug approval process (in contrast to nonphysician mental health clinicians who may perform routine assessments of medical decision-making), and appreciate the risks of coercion discussed in cases like *Kaimowitz*. Under right-to-try laws, the requesting physician currently serves in the role of gatekeeper with respect to attesting to informed consent and the appropriateness of the investigational treatment request. Whether it is through direct or indirect involvement, psychiatrists should have a voice at the table in crafting ways to protect vulnerable patients in this setting. Although not the focus of this editorial, psychiatrists, of course, can also help patients facing terminal illness, end-of-life decisions, and those seeking investigational treatments cope with co-occurring mental illness and stressors to navigate clinical management.

Conclusion

The goal of right-to-try laws is laudable: to improve longevity for patients with serious or terminal illness. These laws raise many complex ethics-related concerns, however, and there are real risks to patients who seek investigational agents under these laws, as well as to the public. The FDA's expanded access provisions reflect an effort to strike a balance between the desire to seek investigational agents and patient protections. The FDA and IRB approval requirements traditionally stand to safeguard minimal safety expectations, including informed consent. In contrast, the right-to-try laws, by removing the requirements of FDA and IRB approval, also remove an important layer of patient protection.

There is no simple answer to the question of what is needed to demonstrate voluntary and informed consent to an investigational agent for which little information is likely to be known. What is clear,

however, is that patients with terminal illness make up a vulnerable population and should be afforded some protections to assure that their participation is voluntary and that they understand the basic risks and benefits of their participation. Reminiscent of the arguments in the right-to-die debate, states have interests in protecting vulnerable patients and preserving the medical profession. Legislatures, institutions, and others who may be involved with access to investigational drugs under right-to-try laws should develop procedures for timely secondary review of the adequacy of the informed consent procedures. Safeguards like IRBs, ethics committees, and other neutral consent reviewers provide benefit to patients and ensure a level of objectivity in the process itself.

References

1. 21 C.F.R. § 312.21 (a) (2006)
2. FDA Clinical Research, updated November 23, 2015. Available at: http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm. Accessed December 16, 2015
3. Hay M, Thomas DW, Craighead JL, *et al*: Clinical development success rates for investigational drugs. Nat Biotechnol 32:41–50, 2014
4. La. Rev. Stat. Ann. § 40:1300.385 (2014)
5. Colo. Rev. Stat. Ann. 25 § -45-107 (2014)
6. Pure Food and Drug Act of 1906, 34 Stat. 768, repealed by 21 U.S.C. § 329 (1938)
7. Drug Amendments Act of 1962, 76 Stat. 780 (1962)
8. Eisenbud M: Medicine and Public Health, in Science, Technology, and the Human Prospect: Proceedings of the Edison Centennial Symposium. Edited by: Starr C, Ritterbush PC. Elmsford, NY: Pergamon Press, 1980, pp 169–76
9. Nichols E: Roundtable for the Development of Drugs and Vaccines Against AIDS. Expanding Access to Investigational Therapies for HIV Infection and AIDS: March 12–13, 1990 Conference Summary. Washington, DC: Institute of Medicine, National Academies Press; 1991
10. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40900 (2009) (to be codified at 21 C.F.R. § 312 (2015))
11. Food and Drug Administration: Individual Patient Expanded Access Application, Form FPA 3926. Guidance for Industry, February 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf/. Accessed December 30, 2015
12. Gaffney A: "Right-to-try" legislation tracker. Regulatory Affairs Professionals Society, June 24, 2014. Available at: http://www.raps.org/Regulatory-Focus/News/Right-to-Try/. Accessed October 1, 2015
13. United States v. Rutherford, 442 U.S. 544 (1979)
14. United States v. Burzynski Cancer Research Inst., 819 F.2d 1301 (5th Cir. 1987)
15. Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007) (en banc)
16. Washington v. Glucksberg, 521 U.S. 702 (1997)
17. Corieri C: Everyone deserves the right to try: empowering the terminally ill to take control of their treatment. Phoenix AZ: Goldwater Institute, February 11, 2014. Available at: https://www.hearland.org/sites/default/files/right-totry-1.pdf. Accessed July 7, 2016
18. Cauchi R: "Right-to-try" experimental prescription drugs: state laws and legislation for 2014 and 2015. National Conference of State Legislatures, available at: http://ncsl.org/documents/health/RighttoTry2015.pdf/. Accessed September 15, 2015
19. Utah S.J.R. 20 (2014)
20. Cal. AB-159 (vetoed 2015)
21. Servick K: "Right to try" laws bypass FDA for last-ditch treatment. Science 344:1329, 2014
22. U.S. Constitution, art VI, cl 2
23. Bolick C. The end of FDA paternalism? Hoover Inst.: Defining Ideas, August 14, 2014. Available at: http://www.hoover.org/research/end-fds-paternalism/. Accessed January 4, 2016
24. Gonzales v. Oregon, 546 U.S. 243 (2006)
25. H.R. 3012 (July 9, 2015). Available at: https://www.congress.gov/bill/114th-congress/house-bill/2012/text. Accessed January 30, 2016
26. Darrow JJ, Sarpatwari A, Avron J, *et al*: Practical, legal, and ethical issues in expanded access to investigational drugs. New Engl J Med 372:279–86, 2015
27. Mackey TK, Schoenfeld VJ: Going "social" to access experimental and potentially life-saving treatment: an assessment of the policy and online patient advocacy environment for expanded access. BMC Med 14:17, 2016
28. Caplan AL, Ray A: The ethical challenges of compassionate use. JAMA 315:979–80, 2016
29. Appelbaum PS, Roth LH, Lidz CW, *et al*: False hopes and best data: consent to research and the therapeutic misconception. Hastings Cent Rep 17:20–4, 1987
30. Sulmsay D, Astrow AB, He K, *et al*: The culture of faith and hope: patients' justifications for their high estimation of expected therapeutic benefit when enrolling in early: phase oncology trials. Cancer 116:3702–11, 2010
31. Penz RD, Whie M, Harvey D, *et al*: Therapeutic misconception, misestimation, and optimism in participants enrolled in phase I trials. Cancer 118:4578–81, 2012
32. Appelbaum PS, Grisso T: Assessing patients' capacities to consent to treatment. New Engl J Med 319:1635–8, 1998
33. Kaimowitz v. Michigan Department of Mental Health, 42 U.S.L.W. 2063 (Mich. Cir. Ct.1973)