Journal of Clinical and Translational Science

ACTS
ASSOCIATION FOR CLINICAL AND TRANSLATIONAL SCIENCE

IMPLEMENTATION, POLICY AND COMMUNITY ENGAGEMENT
EDITORIAL

Right now, in the right way: U. S. Food and Drug Administration's expanded access program and patient rights

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Journal of Clinical and Translational Science (2018), 2, pp. 115–117 doi:10.1017/cts.2018.318

Received 29 May 2018; Revised 25 June 2018; Accepted 27 June 2018

Keywords: Investigational drugs, patient rights, compassionate use, United States Food and Drug Administration, legislation, ethics.

Introduction

Based on approval data, the U. S. Food and Drug Administration (FDA) program that allows for early access to drugs and medical devices before marketing approval, is a very effective means for seriously ill individuals to be treated with investigational agents. Currently the FDA receives, reviews, and approves >99% of over 1000 requests each year [1]. This program is called "expanded access" (EA), also referred to as "compassionate use" [2, 3]. In addition, recent changes in the FDA EA process have streamlined the application to further decrease the timeline and surmount procedural barriers [3]. For individual patient access, a 2-page form is submitted and reviewed within days. If the request represents an emergency, this can be done over the phone (often within hours of the request). The EA approval rate and abbreviated application process suggest that the FDA is not an impediment to patients gaining access to experimental therapeutics. Nonetheless, a United States federal Right-to-Try (RtT) law was passed and signed by President Trump [4, 5]. This legislation, first at the state and now at the federal level, evolved from the efforts of the libertarian Goldwater Institute to make experimental drugs available to patients who seek them by removing oversight of the FDA and local Institutional Review Boards (IRB; ethics committees) [6]. Parties that support the RtT legislation identify the FDA as the primary obstacle to accessing experimental therapies.

What seems to have been lost in the public discussions is a clear presentation of the critical benefits and protections afforded the patient by the current EA system that are missing in RtT (Table 1). Lawmakers and RtT advocates do not appear to understand or acknowledge the inherent risk in experimental therapies, which may have been tested in as few as a dozen patients in a phase 1 trial. Rather than serving as an impediment, the FDA serves as a safeguard for patients facing desperate, complex situations. While much of the current literature focuses on the redundancy and ethical arguments about the legislation [7–10], there are pragmatic and unacknowledged issues surrounding patient rights that are maintained by EA. Importantly, there is a real value to patients that the FDA, as well as other partners in the current EA system, bring to the process. The RtT law, as written, does not preclude the use of the existing EA process. We believe that is very important to make providers aware of EA and that it offers the best option for patients. The FDA, IRBs, and research institutions play critical roles in the EA process by providing patients with the safest possible access to investigational agents.

What role does the FDA play as a valuable component of the EA process? First, because of the requisite confidentiality in the drug development process, the FDA is often the only repository of detailed information about a test agent outside of the manufacturer. This information includes the details of preclinical toxicity, pharmacokinetics, metabolic fate,

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Table 1. *Comparison of patient rights under US Food and Drug Administration (FDA) expanded access program and Right-to-Try law*

Patient concerns	FDA expanded access	Federal "Right-to-Try"
Access to investigational agents	Drugs, biologics, and medical devices	Drugs only
Investigational agent—phase of development	Any stage	Successfully completed phase I
Ethics review	Required. IRB serves as impartial third-party and patient advocate	Not required
Accountability	Physician (investigator/sponsor-investigator) obtains IRB approval, informed consent, reports adverse events, maintains accurate case histories, drug disposition records, and at the end of therapy submits a summary report to FDA. 21 CFR 312.05(c); 21 CFR 312.10(c)(1)	Physician obtains informed consent
Informed consent	Meets federal standards per 21 CFR 50(B) and is reviewed by experienced IRB to ensure requirements are met	No standards stated nor review required
Investigational agent information	Investigator's brochure (meets standards of 21 CFR 312.23(a)5 and ICH E6(R2))	Not addressed
Financial responsibility	Reviewed by IRB and FDA (in the case of charging for the investigational agent)	Not addressed
Site	Follows established workflow per institution	Not addressed
Conflict of interest	Reviewed by independent IRB for coercion, exculpatory language, and financial conflict of interest	Not addressed
Safety reporting to FDA	IND holder is required to report adverse events to FDA	Not required

IRB, Institutional Review Board.

contraindications, and conditions that preclude the use of a drug all contribute to the data that physicians use to safely administer a therapy. There is no such repository required for this information under the proposed RtT system. Often FDA representatives will have knowledge not only about the test agent but also about other agents in the same drug class that may greatly change the assessment of whether or not to use a particular drug. This may allow him or her to offer critical considerations necessary for administering and monitoring an experimental agent as safely as possible. The FDA can and does act as a facilitator of drug access [11].

Another critical component of EA is the accompanying IRB review [12] and the requirement for a rigorous informed consent process. Use of investigational agents is fraught with risk and the probability of benefit is very small. It is known that patients often see only the possibility of benefit without adequate consideration of the improbability of benefit and a very real possibility of harm [13]. Few drugs that start in human studies are ever approved and the earlier a drug is in the development process, the less likely the drug will be shown to be safe and effective [14]. People can suffer extreme side effects and sometimes die from the adverse effects of investigational agents [15]. Patients deserve to have a clear understanding of the risks and likelihood of benefits before proceeding with the use of an investigational agent. This requires a carefully written informed consent document. Providing adequate consent language is difficult, and requires a relatively rare expertise [16]. Established IRBs have extensive experience in reviewing and advising on the informed consent processes and have the expertise necessary to assure that the language is both understandable and accurate. The RtT legislation includes a requirement for "a written informed consent" but, neither the content nor the adequacy of the information is established nor is there a requirement for review for ethical or informational quality. Current EA provisions include an adequate patient informed consent process that conforms to both federal as well as accepted ethical standards and most importantly includes review by an IRB. Desperately ill patients need to be given a realistic picture of their situation. Patients have a right to know and understand what they are undertaking.

Accessing an IRB could be perceived as an impediment in itself. Patients looking for clinical trials will find that EA information is often included in searches at clinicaltrials.gov, patient and disease advocacy organizations, and research institutions. Most EA opportunities will be associated with recognized research institutions such as major academic health centers. These centers have established IRBs familiar with review of informed consent documents that contain the required elements [17]. If use of a local IRB is not feasible, utilization of centralized (independent) IRBs is an option [18]. Recent FDA guidance allows for IRB review of EA with a single reviewer, either the IRB Chairperson or designee [19]. Most established IRBs will have had experience with EA and can serve as an important resource for assuring a timely and authoritative review of the consent document without imposing a barrier to access. In our experience with IRBs at academic health centers, there is typically no charge for review and advice for single patient EA review [10]. Independent IRBs may charge for review of EA requests but, at this time, WIRB-Copernicus Group provides EA IRB review at no charge [20].

Along with the IRB, the value of the institution that supports the physician involved in the EA process is often overlooked. It is difficult to overstate the critical role of the clinical staff at the institution. Many investigational agents are complex to administer, require specialized storage and preparation, and may have profound and serious, even lethal, side effects. Nurses, physicians, and pharmacists familiar with the research use of investigational agents provide an additional safeguard for the patient. For patients seeking investigational agents, the publicly available database of clinical trials, clinicaltrials.gov, provides information for clinical trial sites where EA is available. Most, if not all, of the sites listed will have had extensive experience with the test agents. Further, EA physicians must have "training and experience as

https://doi.org/10.1017/cts.2018.318

appropriate experts" [21] as compared with RtT "be in good standing with the physician's licensing organization or board" [3, 4]. There is irreplaceable value in the experience of the healthcare professionals for the support of a patient receiving an investigational therapy.

The financial burdens for patients of either EA or RtT are not readily comparable. Through the EA program, the company must provide drug free of charge or at cost, as certified by FDA review. RtT places no such restriction on charging for drugs provided through this pathway. It remains to be seen what the monetary impact of RtT will be. For example, at the time of this writing, one company has announced a price of $300,000 for an experimental treatment under RtT [22].

Perhaps part of the argument in favor of RtT stems from the lack of information about how and how well EA works in practice. Since EA occurs mostly in a one-off confidential environment, there is very little information about the actual use of EA beyond the number of EA requests and the drug class along with the FDA Division that ultimately approves the request. The current RtT legislation requires manufacturers to track requests and use. What is critically needed is national data on EA use and outcomes that meets confidentiality and privacy requirements that can inform the development of best practices for EA. The authors, along with other EA regulatory experts, are assembling such a network for that purpose. This network can work to increase awareness of EA as well as facilitate its use. It will be founded based on an existing national IND/IDE work group [10, 23]. This network could direct access to a knowledgeable IRB and experienced institution and create a national network of resources to address equitable access throughout the United States. In addition, the network can accumulate data on the profiles of patients that use EA to better inform the study design of future clinical trials.

Hope is a powerful drug. RtT advocates tell compelling stories of patients fighting for access and invoke the strawman of the FDA as the obstacle to access to investigational therapies. The FDA is not an obstacle. Rather, through the FDA, experienced IRBs, and research institutions, patients already have the right to try and can gain access to investigational therapies in a system that makes their safety and care paramount—one that has no equal in the RtT provisions. If patients choose to receive experimental agents, they deserve to do so in a protective and safe environment that assures access and expediency of IRB reviews, a comprehensive informed consent process, and which assures access to research teams familiar with the safest use of a test agent that already currently exists under EA. The FDA EA program allows patient accessibility to experimental therapies right now, in the right way, and with the right to autonomy and informed consent preserved.

Financial Support

This project was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under awards number UL1TR001105, 1U01TR002488-01 and UL1TR002240. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosures

The authors have no conflicts of interests to declare.

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https://doi.org/10.1017/cts.2018.318