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

M. E. Blair Holbein1*, Kevin J. Weatherwax2, Misty Gravelin2, Raymond Hutchinson3 and George A. Mashour4

1 Department of Clinical Sciences, Center for Translational Medicine, UT Southwestern Medical Center, Dallas, TX, USA
2 Michigan Institute for Clinical and Health Research (MICHR), University of Michigan, Ann Arbor, MI, USA
3 Michigan Medicine, University of Michigan Medical School, University of Michigan, Ann Arbor, MI, USA
4 Michigan Institute for Clinical and Health Research (MICHR), Office of Research, University of Michigan, Ann Arbor, MI, USA

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 1,000 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 I 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. 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, disposition, and safety. The FDA can provide critical insight into the safety and efficacy of a drug, which is essential for making informed decisions about patient care. Additionally, the FDA plays a critical role in ensuring that patient data is protected and that patient privacy is maintained. This is critical for ensuring the safety and well-being of patients participating in clinical trials. Finally, the FDA is responsible for ensuring that clinical trials are conducted in a way that is ethical and safe for patients. This includes ensuring that patients are fully informed about the risks and benefits of participating in a clinical trial and that they are able to make informed decisions about their care.

* Address for correspondence: M.E.B. Holbein, PhD, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9066, USA.
(Email: blair.holbein@utsouthwestern.edu)
includes review by an IRB. Desperately ill patients need to be given an adequate patient informed consent process that conforms to both ethical or informational quality. Current EA provisions include an information is established nor is there a requirement for review for informed consent accurate. The RtT legislation includes a requirement for necessary to assure that the language is both understandable and advising on the informed consent processes and have the expertise to overstate the critical role of the clinical staff at the institution. Many investigational agents include the adverse effects of investigational agents [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

<table>
<thead>
<tr>
<th>Patient concerns</th>
<th>FDA expanded access</th>
<th>Federal “Right-to-Try”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to investigational agents</td>
<td>Drugs, biologics, and medical devices</td>
<td>Drugs only</td>
</tr>
<tr>
<td>Investigational agent—phase of development</td>
<td>Any stage</td>
<td>Successfully completed phase I</td>
</tr>
<tr>
<td>Ethics review</td>
<td>Required. IRB serves as impartial third-party and patient advocate</td>
<td>Not required</td>
</tr>
<tr>
<td>Accountability</td>
<td>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)</td>
<td>Physician obtains informed consent</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Meets federal standards per 21 CFR 50(Bl) and is reviewed by experienced IRB to ensure requirements are met</td>
<td>No standards stated nor review required</td>
</tr>
<tr>
<td>Investigational agent information</td>
<td>Investigator’s brochure (meets standards of 21 CFR 312.23(a5 and ICH E6(R2))</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Financial responsibility</td>
<td>Reviewed by IRB and FDA (in the case of charging for the investigational agent)</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Site</td>
<td>Follows established workflow per institution</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Conflict of interest</td>
<td>Reviewed by independent IRB for coercion, exculpatory language, and financial conflict of interest</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Safety reporting to FDA</td>
<td>IND holder is required to report adverse events to FDA</td>
<td>Not required</td>
</tr>
</tbody>
</table>

IRB, Institutional Review Board.
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, I01TR002488-01 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.

References

2. 21 C.F.R. § 312.305.
17. 21 C.F.R. § 50.20.
20. WIRB. Download forms [Internet] [cited Aug 10, 2018]. (https://www.wirb.com/Pages/DownloadForms/1.aspx)
22. Feurstein A. Here come the right-to-try profiteers. The FDA is powerless to stop them [Internet], 2018 [cited June 20, 2018]. (https://www.statnews.com/2018/06/20/right-to-try-opportunities/)