# Access to Investigational Drugs: FDA Expanded Access Programs or "Right-to-Try" Legislation?

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**Abstract**

**Purpose:** The Food and Drug Administration Expanded Access (EA) program and "Right-to-Try" legislation aim to provide seriously ill patients who have no other comparable treatment options to gain access to investigational drugs and biological agents. Physicians and institutions need to understand these programs to respond to questions and requests for access.

**Methods:** FDA EA programs and state and federal legislative efforts to provide investigational products to patients by circumventing FDA regulations were summarized and compared.

**Results:** The FDA EA program includes Single Patient-Investigational New Drug (SP-IND), Emergency SP-IND, Intermediate Sized Population IND, and Treatment IND. Approval rates for all categories exceed 99%. Approval requires FDA and Institutional Review Board (IRB) approval, and cooperation of the pharmaceutical partner is essential. "Right-to-Try" legislation bypasses some of these steps, but provides no regulatory or safety oversight.

**Conclusion:** The FDA EA program is a reasonable option for patients for whom all other therapeutic interventions have failed. The SP-IND not only provides patient access to new drugs, but also maintains a balance between immediacy and necessary patient protection. Rather than circumventing existing FDA regulations through proposed legislation, it seems more judicious to provide the knowledge and means to meet the EA requirements. Clin Trans Sci 2015; Volume 8: 526–532

**Keywords:** Phase I, new agents, FDA, trials

## Introduction

Access to drugs that do not have approval for marketing by the US Food and Drug Administration (FDA) was recently brought to the forefront of public awareness. From a popular Hollywood movie to numerous compelling stories of individuals who have attempted to obtain experimental treatments, the issue has become both a media and legislative focus.[1–3] Four state legislatures—Colorado, Louisiana, Missouri, and Michigan—have passed "Right-to-Try" bills that include provisions to circumvent FDA approval for use of unapproved drugs.[4–7] Arizona voters passed a similar referendum.[8] Additional legislation has been proposed at both the State and Federal levels.[9] Given this increased public awareness, it is likely that many physicians, particularly those caring for patients with life-threatening illnesses, for example cancer, infectious disease, or neurologic conditions, will encounter questions about access to investigational drugs. In this review we present information about both the FDA's Expanded Access (EA) program[10] and "Right-to-Try" legislation including a comparison of key elements. This review also provides direction and resources to the physician and the institution for working within FDA regulations. This approach can not only provide patient access to new drugs, but also maintains necessary patient protections and permits continued data collection for future users of the product.

## Legislation and Regulations

### "Right-to-Try" legislation

The impetus for the so-called "Right-to-Try" legislation has been fueled by a spate of stories chronicling terminally ill patients who were denied access to experimental drugs.[1–3] These new laws allow physicians and patients to bypass FDA review and approval and do not require review by an ethics committee for the use of experimental treatments. Moreover, these bills do not provide any requirement for pharmaceutical companies to (1) provide the product, (2) set up a clinical study to test the product, (3) change the inclusion and exclusion criteria for current clinical studies, (4) provide product at an affordable price, or (5) incentivize insurance companies to cover the cost of the product. Also included in most of the legislation is a requirement for the patient to sign an informed consent form, but the adequacy of the disclosure is not reviewed. Most of the bills also include indemnification as well as exculpatory language for the informed consent document, which is contrary to usual standards for informed consent.[11,12] *Table 1* provides a comparison of key differences in the existing FDA program and the proposed statutory language for "Right-to-Try" legislation.[1]

### EA to investigational drugs

Much of the proposed legislation as well as public commentary on the topic reveal a profound lack of understanding about the existing means to obtain investigational treatments.[2,13] Currently, the FDA's EA program (see *Box 1* for a summary) seeks to strike a balance in providing access to unapproved drugs and treatments, protecting patients from unreasonable toxicity or danger, and collecting safety data from patients as they take new medications.[14,15] EA, sometimes informally referred to as "Compassionate Use," is different from a standard investigational drug study in that it is not primarily intended to obtain safety and efficacy data but was specifically written to allow use of these agents for treatment of patients outside of a clinical trial in a prescribed manner.[14] The FDA EA program receives about 1,000 EA requests per year and approves over 99% of such requests (*Figure 1*).[16] This should not be interpreted that all requests for such access are always granted.

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| | Expanded access to investigational drugs for treatment use 21 CFR 312.300 (single patients 21 CFR 312.310) | "Right-to-Try" proposed statutory language from Goldwater Institute |
|---|---|---|
| Oversight | FDA | No agency or board oversight |
| | Institutional Review Board 21 CFR 312.305(c)(4) | No requirement for independent review |
| Eligible patient | "Serious or immediately life-threatening disease or condition" with no comparable or satisfactory alternative therapy 21 CFR 312.300(b) | Terminal disease (an advanced stage of a disease with an unfavorable prognosis and no known cure) |
| | The physician determines that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition | The physician gives a prescription or recommendation for an investigational drug, biological product, or device; and in consultation with the patient considers all other treatment options currently approved by the FDA |
| | FDA determines if the potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated | |
| Duration | Treatment usually limited to a single course or specified duration of therapy unless otherwise authorized 21 CFR 312.10(c)(1) | No limits stated |
| 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 | Required. CFR 50.25 (parallels CFR 46.116 Protection of Human Subjects) 8 required and 6 possible additional elements | Required no prescribed content. Notable exception: Colorado and Michigan have seven required elements |
| | IRB reviews and approves the informed consent document assuring accuracy, understandability, and completeness | No review specified |
| Costs | Manufacturer may charge if CFR 312.8(c) parameters met; FDA must approve | Manufacturer may charge |
| | No requirement for insurance company or governmental heath care program to provide coverage | No requirement for insurance company or governmental heath care program to provide coverage |
| Liability | Not addressed | Bars action by medical licensing boards against prescribing physician based on recommendation of investigational agent. |
| | | Criminalizes blocking access to the investigational agent (misdemeanor) |
| | | Note, Colorado and Michigan legislation includes additional indemnification for the manufacturer of the investigational agent. |
| Investigational drug definition | New drug or biological drug that is used in a clinical investigation | Drug, biological product or device which has successfully completed Phase 1 of clinical trials, but has not been approved for general use by the FDA and must currently be under investigation in an FDA clinical trial |
| Drug/device quality | Manufacturing standards established and reviewed in the IND. 21CFR 312.305(b)(2)(vi), (vii) | Not addressed |
| Drug/device information | If available, an investigator's brochure with information from the manufacturer about drug administration and monitoring for known toxicities and adverse effects provided to the treating physician and IRB of record | Not addressed |
| Drug/device availability | Determined by manufacturer; not mandated | Determined by manufacturer; not mandated |
| Impact on future research | Provision of the investigational drug should not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval or development of the agent. 21 CFR 312.305 (a)(1) | Not addressed |
| Timeframe | Emergency: hours to days; 30-day window on IND but usually shorter | No delay |

**Table 1.** Comparison between the FDA expanded access to investigational drug as applies to individual patients and the proposed "Right-to-Try" statutory language (Goldwater Institute).

### Box 1. Expanded Access Summary

Expanded Access (EA), often called "Compassionate Use," is a way to use an investigational drug or biologic that is not approved by the FDA and is given outside of a research study. Occasionally, there are situations where a patient with a serious or immediately life-threatening disease has no alternative treatment options. In these cases the investigational drug is expressly used for the treatment of patients and not for study of the drug. Under EA the FDA allows such use for either individual patients or for larger size groups. The process is governed by federal regulations (21 CFR part 312.300).

EA begins with agreement between the manufacturer/sponsor to supply the drug and the treating physician. These arrangements must be authorized by the FDA through an Investigational New Drug (IND) Application. The IND is a structured presentation of the information needed to use the drug in a human patient. Investigational drugs have significant risks to the patient that must be taken into account and oversight by an Institutional Review Board (IRB or Ethics Committee) is also required.

Manufacturers *are not required* to set up these EA protocols. They are *not required* to supply the drug nor manufacture more drugs to meet a larger need.

While the FDA tries to accommodate the needs of the patient, occasionally there are variations in the acceptable risks that might not be apparent to the public. The FDA has access to safety data and has expertise to make assessments as to "reasonableness" of the proposed use. The FDA often works closely with the manufacturer to avail the product to the patient under these circumstances.[13,17] Nevertheless, in some instances—despite FDA approval—the company owning the product may decline to provide it outside the context of a formal clinical study.

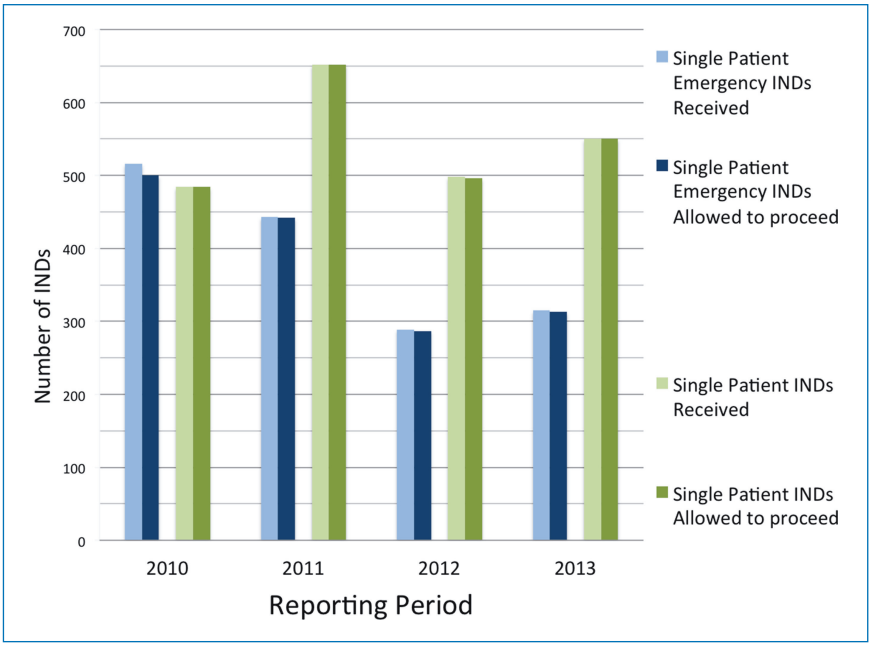


**Figure 1.** FDA expanded access program, activity reports data for single patient INDs shown. Filings for other expanded access INDs and protocols were much smaller in number and are not shown. Approval rate exceeded 99% for all other categories.[13] Inclusive dates for reporting periods: 2010 (10/13/09–10/12/10), 2011 (10/13/10–10/12/11), 2012 (10/01/11–09/30/12), 2013 (10/01/12–09/30/13).

**Patient eligibility and roles for EA**

The FDA has clear regulations that define patient eligibility for the EA program. The criteria generally include patients with an immediately life-threatening disease or condition with a substantial risk of mortality or premature death occurring within a window of months and who have no satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.[10] The EA process has several means of access and multiple submission pathways. *Table 2* provides the defining criteria, including the number of patients to be treated, potential access to an existing study being conducted under an Investigational New Drug (IND) application and whether there is a need for emergency treatment. Applications that are made under current INDs are mediated through the IND sponsor who for novel therapies is usually the manufacturer. In these cases the use is obtained by an amendment to an existing IND and is referred to as a "protocol amendment IND." Alternatively, when one person takes on the roles of both the regulatory "Sponsor" as defined by the FDA and as the physician who administers the investigational drug, he or she becomes a "Sponsor–Investigator," a role which includes the analysis of the lack of therapeutic options, filing the IND, as well as obtaining the approval of an Institutional Review Board (IRB). Importantly, for Sponsor–Investigators additional regulatory obligations such as ongoing reporting to the FDA do not end until the IND is withdrawn.[18] *Figure 2* provides a flowchart to guide the physician regarding which type of submission pathway is most applicable.

**EA for an individual patient through the Single Patient-IND**

In both academic health centers and in community-based physician practices, the most frequently encountered EA category is the Single Patient-IND (SP-IND) application. Enrollment of a patient in a clinical trial may not possible due to geographic location, stringent eligibility criteria, or timing of the trial. In such cases, through the SP-IND mechanism, the FDA permits an investigational drug to be used for the treatment of an individual patient suffering from serious or immediately life-threatening disease or a condition for which there is no satisfactory approved therapy. The treatment under the SP-IND is generally limited to a single course of therapy for a specific duration, although the FDA may authorize multiple courses or chronic therapy. For example, treatment may be approved until either disease progression, intolerable toxicity, or patient/provider preference. Commercial availability may also result in an early conclusion of the IND. There are both nonemergency and emergency versions of the SP-IND (*Table 2*).

Applying for a nonemergency SP-IND follows the standard IND application regulations (see *Box 2*, SP-IND Submission).[19] The essential first step in an SP-IND is working with the manufacturer

| Type of extended access (EA) IND | | 21 CFR 312.300 | Number of patients | FDA review time | IRB approval | FDA approval | Course of therapy |
|---|---|---|---|---|---|---|---|
| Single patient-IND/ protocol amendment | Nonemergency use | §312.310 | 1 | 30 days | Approval needed prior to treatment | Approval needed prior to treatment | Usually 1 |
| | Emergency use | §312.310(d) | 1 | Urgent | Report within 5 days | Approval prior to treatment; report within 15 days | Usually 1 |
| Intermediate size patient population IND/protocol amendment | N/A | §312.315 | Smaller than typical Treatment IND (usually < 100) | 30 days | Approval needed prior to treatment | Approval needed prior to treatment | Defined in protocol |
| Treatment IND/ protocol amendment | N/A | §312.320 | Written into protocol | 30 days | Prereported | Prereported | Defined in protocol |

Notes: Under the FDA's EA program, there are several regulatory strategies available and the best one to use will depend on the particular factors for each situation. This table lists some of the key factors to consider when choosing which strategy to employ. In each of the four types of EA pathways, the use of protocol amendment submitted to an existing IND is the most straight-forward and entails the least regulatory submission burden.

**Table 2.** Characteristics of expanded access (EA) INDs.

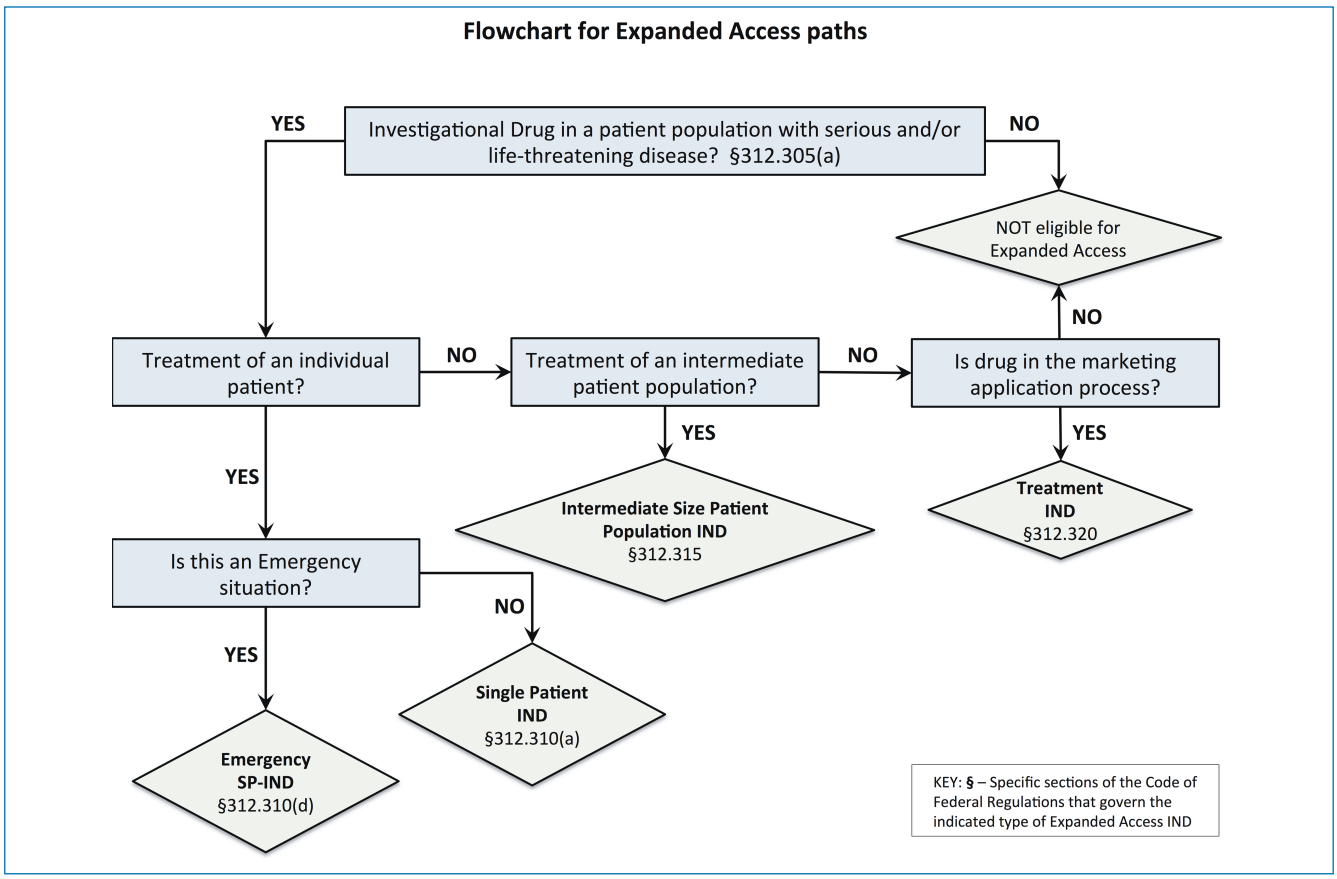


**Figure 2.** Flowchart for expanded access paths.

to obtain drug. Most of the product information needed in the IND is supplied as a reference to existing manufacturer-supplied data. The treating physician will have the necessary information about the patient readily available as part of the medical record. Although the statutory 30-day FDA review period applies, in many cases the process is expedited. Notably, all of the usual "life cycle" IND maintenance activities, such as safety and annual reporting as well as submission of amendments, still apply.[18]

Emergency SP-INDs include life-threatening circumstances where no alternative is available and there is no time to prepare a written submission to the FDA. In these infrequent and extraordinary situations the physician may treat the patient prior to FDA notification. Nevertheless, all attempts should be made (if time allows) to obtain any feedback from the FDA via phone, e-mail or fax before the treatment.[19,20] If time does not allow for any feedback, the physician is allowed to proceed with the

**Box 2. Expanded Access, Single Patient-IND Submission Contents**

1. FDA Form 1571—structured presentation guide for the needed information. (Search "FDA Forms" to find FDA Form Website).
2. Statement of the rationale for using the drug. Include a list of the available options and an explanation of why the investigational agent is preferable or the only therapeutic option.
3. Description of the individual patient's disease or condition. Include medical history, description of previous treatments, and sufficient information to make the rationale for requesting the investigational clear.
4. Description of the intended method of administration of the drug including dose and duration of therapy.
5. Reference the manufacturer's "Chemistry, Manufacturing, and Controls" information. This will require permission and cooperation of the manufacturer to provide this information, usually as a cross-reference to an existing FDA file.
6. Reference the manufacturer's "Pharmacology and Toxicology Information." This will require permission and cooperation of the manufacturer and usually cross-references an existing FDA file.
7. Description of plan to evaluate the effects of the drug and minimize the risks. This will include clinical procedures, laboratory tests, or clinical assessments as needed. Include the proposed patient Informed Consent document and the plan for monitoring for adverse effects.
8. FDA Form 1572—statement of the qualifications of the investigator (usually the treating physician). An academic curriculum vitae or the equivalent is sufficient.
9. Clearly mark the submission cover sheet and the mailing envelope as "EXPANDED ACCESS SUBMISSION."

necessary investigational treatment and report it to the FDA later within the required time frame.[21] By utilizing the Emergency IND submission pathway, the FDA allows access of an investigational drug to the patient in an extremely short time period, while still providing necessary oversight. It is also important to note that this scenario which aims for the fastest available treatment, would equate to the Right-to-Try legislation, but maintains oversight and accountability.

**EA for intermediate-size population and Treatment IND**

When there are a number of individual patients with the same disease or condition, the FDA may ask the sponsor to consolidate SP-INDs under an intermediate-size patient population IND (21 CFR 312.315). This might apply if the drug is not being actively developed, or if the patient population is too small, as in the case with rare diseases. As for all EA types of INDs, in order to be eligible for drug access under an intermediate-size patient population IND, the FDA must determine that the conditions listed in the regulations are met and that the risk/benefit ratio has been assessed and justified. Finally, if a drug has been removed from the market due to safety reasons, there might be a situation calling for an intermediate-size IND.

The Treatment IND allows patients to access a drug that is currently being reviewed under an FDA marketing application, but has not yet received FDA approval (21 CFR 312.320). Here safety and efficacy data have already been collected and submitted to the FDA and are undergoing review for marketing approval. A Treatment IND is sponsored by the company seeking marketing approval and can provide drug access to hundreds to thousands of patients while FDA review for final approval is underway. Patients must still meet eligibility criteria, and during the course of the study data will continue to be collected and used to expand the current knowledge about the drug.

**Using the access process**

For both the physician and the patient it is essential to understand that the best access to an investigational drug is by participation in a clinical trial. Before considering EA, every effort should be made to find a clinical trial for the patient through clinical trial databases (such as clinicaltrials.gov), working with patient advocacy groups, or making inquiries to the manufacturer or the FDA. Established clinical trials have been reviewed carefully to ensure the best utilization of the investigational drug and the most comprehensive ethics review. Also the most accurate and rigorous data collection will take place under a clinical trial to inform its use in other patients and to guide future indications. Not infrequently, this would also be the most timely and least costly route for the patient, as well as provide the most equitable access.

**Pharmaceutical sponsors and EA**

The necessary first step in any EA process is to obtain access to the drug. The most direct approach is to contact the manufacturer. Research personnel from the manufacturer that the investigator has worked with previously may be able to expedite contact with the appropriate individuals at the manufacturer. Alternatively, most manufacturers have contact information on their Websites. In the case of a call to a manufacturer it is important to make clear the intent of the call is to contact the research personnel familiar with the test agent. In either case the physician should be able to readily provide information about the circumstances that make EA the best option for the patient. This includes the clinical status of the patient and the appropriateness of the test agent for that patient. Contact with the FDA may also expedite the process if attempts to contact the manufacturer are not successful. A list of contact phone numbers for the appropriate Office or Division is maintained on the FDA Website.[19] Sometimes the FDA can assist in the process of making drug available. They may also help in guiding the investigator to provide the information needed by the FDA to understand the clinical status of the patient.

**Institutional Review Boards and EA**

The administration of any investigational drug under the auspices of an IND also requires approval by an IRB.[14] Because of their

situation, patients with life-threatening conditions are a "vulnerable population" who especially need the protections provided by an IRB. A central role for the IRB is assisting the Sponsor–Investigator in assuring that an adequate informed consent process occurs. To address a possible therapeutic misconception that the likelihood of the perceived benefit is greater than it may actually be, the informed consent document should include an explicit statement of the experimental nature of the therapy, the unknown likelihood of benefit and risk, and a comprehensive explanation of any alternative therapies. Some IRBs may not be familiar with the EA process and may not understand that the intent is explicitly treatment and not research. The choice of EA implies that the investigator has made a clinical judgment that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition.[14] The IRB should rely on the assessment of the clinician as well as medical records included in the request as to the status of the patient and the immediacy of the need to treat. An important difference for an IRB to consider when reviewing an EA request is that information available about the investigational drug might be substantially less than would usually be available for IRB deliberations. The supporting data needed for use in a single patient with a life-threatening condition is significantly less than would be required for use in larger population IND. The risk-benefit calculus that is usually an essential part of an IRB deliberation is markedly different for an SP-IND.

Regulations currently require an IRB to conduct a full board review, which can present the possibility of administrative delays. However, IRBs at most major medical centers usually have a process in place for handling emergency as well as nonemergency SP-INDs in accordance with FDA regulations. In contrast, small or community-based healthcare system IRBs may not be familiar with the EA process; nor can they quickly assemble to review such a request. The possibility of developing reciprocity with a regional IRB, such as at an academic medical center within reasonable proximity, or taking part in a central IRB that has experience with such protocols may be an option for some sites.[22]

## Available resources for EA

There are numerous resources available to assist in the preparation of the EA IND. The FDA maintains an easily navigable Website.[23] Enlisting the help of regulatory specialists can greatly assist in understanding and completing the needed documentation. A survey of U.S. academic health centers across the country showed that the majority of them have offices with dedicated IND specialists to assist with these processes.[24] Informal polling within these offices indicates that nearly all provide specific services for EA INDs without charge. Finally, since IRB approval is needed, contact with the IRB of record should be made early in the process.

## Discussion

The existing FDA EA program was specifically written to provide an effective means to access investigational drugs while maintaining a balance between subject safety and access. Central to EA is the voluntary involvement of the company that manufactures the drug or biologic; without their active participation the product cannot be considered for any of the processes discussed in this paper. When a physician analyzes how best to provide access to investigational drugs, the pathway is driven by several factors: (1) the number of patients needing access, (2) the time sensitivity of access (emergency or not), (3) whether an active IND is in place by which a protocol amendment can be filed or not, (4) whether or not the existing IND can be extended to the patient, and (5) availability of an IRB with administrative authority and familiarity with the EA process. For an individual patient and his or her physician, the best course of action is often a SP-IND.

Another factor relevant to these requests is how the infrastructure within a medical center can support the processing of such submissions. Availability of a regulatory support office to guide the physician through the SP-IND process is beneficial but not imperative. As outlined above, an individual physician has all the information necessary to submit for EA to the FDA on his or her own, but many centers do provide support, usually without charge. IRBs should be encouraged to develop processes to accommodate all forms of EA to investigational drugs. With appropriate education, guidance, decision tools and templates, IRBs and physicians can become well equipped to manage requests for EA. We would encourage such centers to consider waiving usual IRB fees for this application unless the volume becomes burdensome. This is especially appropriate if the manufacturer is providing drug at no charge. Equitable access to EA should be a consideration as a part of the mission that many serve. For physicians not in a relationship with an academic medical center, the use of a central IRB can serve that important patient-safeguard role. IRB participation is a critical difference between EA and "Right-to-Try" legislation.

"Right-to-Try" legislation is an attempt to expedite the access to test agents by creating loopholes to bypass the current federal oversight process and IRB or ethics committee review. This effort suggests that members of the general public and some lawmakers underappreciate the tenuous nature of drugs in development. Very few drugs make it through the entire research pipeline to approval for good reason. For investigational products that are still in early testing up to and including Phase 3 trials, potential adverse events are not known yet, efficacy is not established, and there is a very real possibility that harm exceeds risk. "Right-to-Try" legislation leaves a vulnerable population open to unproven and potentially dangerous treatments. Abolishing the federal oversight will not solve the dilemma of getting investigational products safely to patients more quickly. It seems more prudent to arm physicians and their staff with knowledge and skills to meet the existing EA program requirements that allow access to investigational agents for seriously ill patients. The EA program provides a measured approach for access to unapproved treatments balanced with a conscious and informed consideration of the risks for patient.

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