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Implementation of 21st Century Cures Act Expanded Access Policies Requirements

Sukhun Kang¹, Sungyong Chang¹, Joseph S. Ross^{2,3} and Jennifer E. Miller^{2,*}

The US Food and Drug Administration (FDA) expanded access pathway allows patients with life-threatening or serious conditions to access investigational drugs outside of trials, under certain conditions. The 21st Century Cures Act (“Cures Act”) requires certain drug companies to publicly disclose their expanded access policies. We characterized the proportion of applicable US biopharmaceutical companies, with an oncology related drug, implementing Cures Act requirements for expanded access policies and whether available policies contain the information described in the Act. We found about one-third of applicable biopharmaceutical companies (32%, 140/423) implemented the Cures Act requirement to have a public expanded access policy. Less than one-third of public policies contained all described information (31%, 44/140). Larger companies and those with at least one drug receiving an FDA expedited designation (59% vs. 21%; $P < 0.001$), or at least one FDA-approved drug (57% vs. 28%; $P < 0.001$) were more likely to have a public policy. Our results suggest the Cures Act may be having a limited impact on its goals of supporting timely medical decisions and closing informational gaps for patients and doctors around expanded access to investigational oncology therapies, especially for products sponsored by smaller and newer companies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ The US Food and Drug Administration (FDA) expanded access pathway allows patients with life-threatening or serious conditions to access investigational drugs outside of trials, under certain conditions. The 21st Century Cures Act (“Cures Act”) requires certain drug companies to publicly disclose their expanded access policies, to help support timely medical decisions and close informational gaps for patients and doctors looking to access experimental treatments outside of clinical trials. Only one study to date, to our knowledge, has analyzed implementation of the Cures Act expanded access policy requirements, but it focused on a much narrower company sample generally large companies and those with an FDA-approved drug. Analyzing 45 companies, they found a high implementation rate at 76%.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ What proportion of applicable US-based oncology companies implement the 21st Century Cures Act requirements for

having a publicly available expanded access policy and what company characteristics are associated with implementation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Analyzing 423 companies, we found 32% (140/423) had a public expanded access policy and less than one-third of the public policies contained all required information (44/14).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ These results suggest the Cures Act may be having limited impact on its goals of supporting timely medical decisions and closing informational gaps for patients and doctors looking to access experimental oncology treatments outside of clinical trials, through expanded access, especially for experimental products sponsored by smaller and newer companies.

The US Food and Drug Administration (FDA) expanded access (EA) pathway, sometimes also called compassionate use, is a route for patients with immediately life-threatening or serious diseases or conditions to potentially access experimental medicines outside of clinical trials. To qualify, patients must be unable to enroll in a relevant clinical trial, have no comparable satisfactory alternative FDA approved therapy options, and be deemed more likely to experience benefit than risk from the unapproved

intervention. Additionally, expanded access provisions should not threaten a product's development program (e.g., trial enrollment). Formalized in 1987, in the context of the AIDS epidemic, the EA pathway has been amended multiple times, most recently in 2016 through section 561 of the Food, Drug, and Cosmetics Act (FDCA), as a part of the 21st Century Cures Act (“Cures Act”).

The Cures Act aimed to help increase awareness among patients and clinicians about the processes and procedures for accessing

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investigational medical products outside of clinical trials, by requiring certain drug companies to develop and publicly disclose their EA policies, for example, by posting them on their websites. The Act also describes five informational elements for the contents of the policies, related to who and how to contact the company with a request as well as the criteria and timeline used by the company for evaluating and responding to such requests. Although having a publicly available policy does not guarantee a patient will ultimately receive a requested investigational oncology therapy, the Act aimed to increase the transparency and accessibility of company policies to better support physicians and patients in making timely medical decisions.¹

Whereas EA pathways can involve the participation of and approval from a physician, the FDA, and an institutional review board, the sponsor developing each product ultimately has a final gatekeeping power to grant or deny an access request. These sponsors are typically, although not always, biopharmaceutical companies, which vary substantially in size, revenue, and age. To date, only two studies have assessed implementation of the Cures Act requirements to have a publicly available EA policy. Reviewing small samples of 45 and 100 pharmaceutical companies, respectively, they found 76% and 47%, respectively, had publicly available EA policies.^{2,3}

Our paper aims to extend these studies to newly include all drug companies headquartered in the United States, with an oncology focus, that are highly likely subject to the Cures Act. This sample is defined as US-based companies with at least one oncology drug in or beyond phase II in clinical trial development, or with at least one oncology drug that received a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection by the FDA. This scope expansion involves uniquely, including all sized companies, private companies, companies without approved drugs but conducting or sponsoring an applicable phase II or later stage oncology clinical trial, and companies with at least one drug having received an FDA expedited program designation. We also review each publicly available EA policies for inclusion of the five categories of information described inclusion by the Cures Act and evaluate company characteristics, such as private versus public, size, and revenue, associated with having a publicly available EA policy.

We focus on companies with an oncology product for several reasons. First, oncology is the most common represented disease target for expanded access programs registered on clinicaltrials.gov through July 1, 2016.⁴ Second, two new projects intended to improve the information available about EA were recently launched in oncology. The first is “Project Facilitate,” a program run out of the FDA’s Oncology Center of Excellence, which assists clinicians in navigating expanded access pathways for patients with cancer.⁵ The second one, run by the Reagan-Udall Foundation for the FDA, is an expanded access navigator, providing a step-by-step guide for accessing investigational therapeutics geared toward patients and caregivers as well as clinicians.¹ Whereas the navigator ultimately intends to cover multiple therapeutic areas, its initial phase was focused on oncology. We expect our findings will inform policymakers on oncology companies’ transparency in terms of their expanded access policies and on information gaps

in supporting doctors and patients in making informed and timely medical decisions.

METHODS

Data sources

Data were abstracted from the Pharmaproject,⁶ a large commercial database of global pharmaceutical research and development, Medtrack, a commercial database of global pharmaceutical companies, and Crunchbase, an online database for companies.

Study sample

We included all biopharmaceutical companies with a US headquarters and an oncology focus (“US-based oncology companies”), that are highly likely subject to the Cures Act, which are generally companies with at least one oncology drug in or beyond phase II in clinical trial development, or with at least one oncology drug that received a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection by the FDA. Companies without a US headquarters and subsidiaries of companies with US headquarters were excluded. See **Table 1** for more company inclusion criteria and policy requirements under the Cures Act.

Data collection

We identified all applicable US-based oncology companies by searching Pharmaproject for US-based oncology drug companies with at least one oncology drug beyond phase II in clinical trials, as well as those with at least one drug which received FDA expedited program designation. We then characterized drug companies by type (publicly traded or private), age, number of employees, annual revenue, and development status from Medtrack and Crunchbase. Unless otherwise noted, missing values were excluded from the analysis.

We manually searched every applicable company’s website to identify and collect publicly available expanded access policies. If we could not find an expanded access policy on a company’s website, we also conducted an internet search (using Google) and searched the FDA’s Expanded Access Navigator for a public policy.¹ For the internet search, we used a company name followed by the following keywords: “expanded access,” “compassionate use,” “early access,” and “pre-approval access” to find policies.

For available EA policies, we manually extracted policy characteristics, including the five pieces of information described for inclusion in policies by the Cures Act (see outcome measures). To ensure the robustness of our data, two research assistants conducted two independent data collections. We also extracted company characteristics, including company age, company type (publicly traded or private), number of employees, and annual revenue from Pharmaproject, Medtrack, and CrunchBase. All data were collected in June 2020.

Outcome measures

Our primary outcome measure was whether a drug company had a publicly available EA policy on its website. Secondarily, for available EA policies, we assessed the proportion of policies containing five pieces of information described by the Cures Act related to: (i) whom to contact; (ii) the process for requesting EA to a product at the company; (iii) the anticipated time the company will take to acknowledge receipt of a request; (iv) the criteria it will use to evaluate such requests; and, finally (v) whether the policy links to or references the clinical trial record on ClinicalTrials.gov (see **Table 1** for more details).

In addition, we also examined (i) whether each company had a separate webpage for their expanded access policy, (ii) how easily accessible the information was (i.e., number of clicks from the main webpage), (iii) whether the policy followed the structure of one of the sample policy structures posted by the FDA on Expanded Access Navigator,⁷ and (iv) terminology used for EA.

Table 1 The 21ST Century Cures ACT (Section 561 of the Food, Drug, and Cosmetics Act) and corresponding outcome measures used in the study

	Wordings from the act	Outcome measures
Applicability condition	i. The first initiation of a phase II or phase III study (as such terms are defined in section 312.21(b) and (c) of title 21. Code of Federal Regulation (or any successor regulations)) with respect to such investigational drug	FDA Expedited Programs (Tables 2, 4)
	ii. An applicable, 15 days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection (a), (b), or (g), respectively of section 356 of this title	
Content of policy	Contact information for the manufacturer or distributor to facilitate communication about requests described in subsection (a)	<i>Policy Content #1</i> Contact information
	Procedures for making such requests	<i>Policy Content #2</i> Request procedures
	The general criteria the manufacturer or distributor will use to evaluate such requests for individual patients, and for responses to such requests	<i>Policy Content #3</i> Criteria for evaluating requests
	The length of time the manufacturer or distributor anticipates will be necessary to acknowledge receipt of such requests	<i>Policy Content #4</i> Time to acknowledge receipts
	A hyperlink or other reference to the clinical trial record containing information about the expanded access for such drug that is required under section 282(j)(2)(A)(ii)(I)(gg) of title 42	<i>Policy Content #5</i> Clinical trial record

FDA, US Food and Drug Administration.

Finally, to assess whether company characteristics are associated with Cures Act implementation, we divided companies into groups: publicly listed vs. private companies; top 50% vs. bottom 50% in median annual revenue; top 50% vs. bottom 50% in median number of employees (large vs. small), top 50% vs. bottom 50% in median company age (older vs. newer). A detailed description of how we coded each variable is available in Appendix S1.

Statistical analysis

Frequencies and proportions are reported for our outcome measures. We used the Wilcoxon test to examine differences in the average value of compliance rate and counts of contents posted across two groups based on company characteristics. We reported the differences in mean alongside the 95% confidence interval and the two-sided *P* value, which indicates statistical significance (*P* < 0.10 were considered as statistically significant). All statistical analyses were performed using Stata statistical software version 15.0 (StataCorp LLC).

RESULTS

Study sample characteristics

We identified 423 US-based drug companies with at least one oncology drug beyond phase II in clinical development or which received FDA expedited program designation, such as FDA fast-track or breakthrough therapy designations. The majority of the sample (63.6%, 269/423) were private companies and the rest were publicly traded companies in the United States. About half of companies (53%, 216/423) were < 10 years old, 32% < 5 years old, and 21% 6–10 years old. Just over half, (52%, 184/423) had 50 or fewer employees (19% had 1–10, 33% had 11–50). About 23% (72/423) of companies reported < \$1 M in annual revenue, 38% (118/423) \$1 M and \$10 M, and 12% (38/423) over \$100 M. About 29.2% (128/423) of companies had received the FDA expedited program designations, and 11.19% (49/423) of them had at least one product approved for use by the FDA (see Table 2).

Implementation of Cures Act expanded access policy requirements

Among our study sample, 32.0% (140/423) of companies had a publicly available EA policy. Of these, 31.4% (44/140) contained all of the 5 elements described by the Cures Act. Specifically, 82.1% (115/140) explained whom to contact at a company with an EA request, 72.1% (101/140) contained the anticipated time the company takes to acknowledge receipt of an EA request, 72.9% (102/140) indicated the process for requesting EA to a product from the company, 59.7% (83/140) included the criteria used by the company for evaluating requests, and 55.1% (76/140) linked to or referenced a clinical trial record on ClinicalTrials.gov. Five days was the most common stated response time for acknowledging receipt of an EA request (49.4%, 41/83). Most of these policies (82.2%, 115/140) were located on a separate webpage exclusively on EA within a company's website. It required at least 2 clicks from a company's landing homepage to reach the EA policies for 72.0% (95/140) of companies with policies. About half of the available policies (50.7%, 61/140) followed a structure one of the policy samples posted by the FDA.⁷ Last, 60% (84/140) of the policies used the term "Expanded Access," but there were wide ranges of other terminologies also used, including "Compassionate Use" (12.9%, 31/140) and "Early Access" (2.1%, 5/140; see Table 3).

Company characteristics associated with Act implementation

Companies that were publicly traded (49% vs. 24%; *P* < 0.001), had above the median number of employees (47% vs. 26%; *P* < 0.001), and greater annual revenue (49% vs. 32%; *P* = 0.003) were more likely to have publicly available EA policies. In addition, companies that had FDA expedited program designations (59% vs. 21%; *P* < 0.001) and companies that had an

Table 2 Characteristics of study sample^a

Characteristics	Study sample (N = 423)
Disclosure of expanded access policy	
Yes	140 (32.0)
No	298 (68.0)
Company type	
Public	154 (36.4)
Private	269 (63.6)
Company age	Median = 14 years
0–5	131 (31.7)
6–10	85 (20.9)
11–15	77 (18.6)
16–20	42 (10.2)
21–25	17 (4.1)
26+	61 (14.8)
Number of employees	Median = 50 employees
1–10	66 (18.7)
11–50	118 (33.4)
51–100	53 (15.0)
101–250	53 (15.0)
251–500	21 (6.0)
501–1,000	15 (4.3)
1,001–5,000	8 (2.3)
5,001–10,000	5 (1.4)
10,001+	14 (4.0)
Annual revenue	Median = \$10 M in annual revenue
Less than \$1 M	72 (23.2)
\$1 M to \$10 M	118 (38.1)
\$10 M to \$50 M	69 (22.3)
\$50 M to \$100 M	12 (3.9)
\$100 M to \$500 M	20 (6.5)
\$500 M to \$1 B	3 (1.0)
\$1 B to \$10 B	12 (3.9)
\$10 B+	3 (1.0)
FDA expedited programs	
Yes	128 (29.2)
No	310 (70.8)
FDA approved	
Yes	49 (11.19)
No	389 (88.81)

FDA, US Food and Drug Administration.

^aPercentages may not total 100 because for each data there is minority of drug companies with missing data.

FDA-approved product (57% vs. 28%; $P < 0.001$) were more likely to have publicly available EA policies. In terms of content posted, older (3.8 vs. 3.0; $P = 0.001$) and larger companies (3.6 vs. 3.2; $P = 0.08$) had a higher number of content items described by the Cures Act in their publicly available EA policies on their websites (see **Table 4**).

Table 3 Main outcome measure^a

Characteristics	Study sample (N = 423)
Disclosure of expanded access policy	
Yes	140 (32.0)
No	298 (68.0)
	Expanded access policies (N = 140)
Policy content	
1. Contact information	115 (82.1)
2. Request procedures	101 (72.1)
3. Criteria for evaluating requests	102 (72.9)
4. Time to acknowledge receipts	83 (59.7)
5. Clinical trial record	76 (55.1)
All	44 (31.4)
Response time	
1 Day	8 (9.6)
2 Days	12 (14.5)
3 Days	2 (2.4)
5 Days	41 (49.4)
6–10 Days	14 (16.9)
11+ Days	6 (7.2)
Separate webpage	
Yes	115 (82.1)
No	25 (17.9)
Number of clicks	
1	22 (16.7)
2	95 (72.0)
3	15 (11.4)
Expanded access policy sample	
1	9 (6.4)
2	60 (42.9)
3	2 (1.4)
Others	68 (48.6)
Expanded access terminology used	
“Access (to investigational drugs)”	11 (4.6)
“Compassionate Use”	31 (12.9)
“Early Access”	5 (2.1)
“Expanded Access”	84 (60)
Combinations of above terms	18 (7.6)
Others (“Managed Access,” “Early Patient Access,” “Patient’s Access”)	30 (12.6)

^aPercentages may not total 100 because for each data there is minority of drug companies with missing data.

DISCUSSION

The 21st Century Cures Act requires certain drug companies to have a public policy (for example, on their website) informing patients and physicians about how they can request expanded access to investigational medical products for life-threatening or

Table 4 Comparison of compliance based on the company characteristics

Outcome measure		Group A	Group B	Difference (95% CI)	P value
Company type		Public	Private		
	Policy disclosure (yes or no)	0.49	0.24	0.26 (0.16–0.35)	0.00
	Policy contents posted (n/5)	3.55	3.26	0.28 (–0.24 to 0.80)	0.14
Company age		Above median	Below median		
	Policy disclosure (yes or no)	0.30	0.34	–0.04 (–0.05 to 0.13)	0.19
	Policy contents posted (n/5)	3.84	2.97	0.87 (–0.37 to 1.37)	0.00
Number of Employees	Policy disclosure (yes or no)	0.47	0.26	0.21 (0.11–0.31)	0.00
	Policy contents posted (n/5)	3.61	3.20	0.41 (–0.17 to 0.99)	0.08
Annual Revenue	Policy disclosure (yes or no)	0.49	0.32	0.17 (0.06–0.28)	0.00
	Policy contents posted (n/5)	3.48	3.44	0.04 (–0.52 to 0.60)	0.44
FDA Expedited Programs		Yes	No		
	Policy disclosure (yes or no)	0.59	0.21	0.38 (0.28–0.47)	0.00
	Policy contents posted (n/5)	3.62	3.21	0.40 (–0.11 to 0.92)	0.12
FDA Approved	Policy disclosure (yes or no)	0.57	0.28	0.28 (0.13–0.43)	0.00
	Policy contents posted (n/5)	3.77	3.33	0.44 (–0.11 to 0.98)	0.11

CI, confidence interval; FDA, US Food and Drug Administration.

serious conditions outside of clinical trials. We sought to determine the proportion of applicable companies that have publicly available EA policies in accordance with Act requirements, company characteristics (e.g., type, age, size, and revenue) associated with enhanced implementation, and the completeness of publicly available policies.

We found about one-third of applicable US-based oncology companies have a public expanded access policy as required. However, only about one in three of these public EA policies contain all of the informational items described by the Cures Act. For instance, one in five failed to provide contact information at the company for submitting expanded access requests. Similarly, two in five policies failed to indicate the criteria the company uses to evaluate EA requests. Larger, older, and publicly traded companies with at least one FDA-approved drug or FDA-expedited program designation were more likely to have a public EA policy.

Only two other studies, to our knowledge, have analyzed implementation of Cures Act requirements to have a publicly available EA policy. Although our study examined a sample of 423 companies, these prior studies focused on samples of 45 and 100 companies and found that 76% and 47%, respectively, had publicly available EA policies.^{2,3} Only one of these studies evaluated the completeness of expanded access policies, finding 42% (19) of policies included all 5 categories of content described in the 21st Century Cures Act. The difference in findings may be due to our inclusion of all applicable US-based drug companies, with an oncology product in at least phase II development, not just those with an FDA-approved drug, and not just public companies. Our finding on Cures Act implementation rates is more similar to other studies evaluating biopharmaceutical companies' compliance with other US laws governing clinical research, such as clinical trial registration and results reporting requirements under the FDA Amendments Act (FDAAA).^{8–10}

Our findings suggest there may be financial and other resource constraints limiting companies' abilities to develop and publicly disseminate EA policies. The findings also suggest that accessing experimental products from smaller and newer companies may be more challenging for patients and clinicians, given these companies are less likely to have publicly available EA policies. This finding is consistent with prior articles on EA, which described several practical, legal, and ethical challenges associated with implementing expanded access.^{11–15} In particular, drug company participation in EA may be limited due to administrative burden, as EA can require significant human resources.¹² There is a need to improve awareness about processes and procedures for seeking EA^{16–18} and better enforce Cures Act EA policy requirements. For example, currently, the Act does not appear to specify a penalty for noncompliance. Providing smaller companies with assistance developing EA policies through existing initiatives like US FDA Small Business Assistance Programs, may help close information gaps for patient and physician communities on pathways for accessing experimental treatments.¹⁹

Limitation

We note limitations to our study. First, our analysis relied heavily on hands-collected data. Whereas the advantage of manual data collection regard the uniqueness of data, the disadvantage is that it may not review all available information. For example, the manual search of each website of 423 companies may not capture the entire history of their compliance on EA policy. Second, our sample excludes companies headquartered outside the United States conducting clinical trials in the United States, which can also be subject to the Cures Act, thereby limiting the generalizability of our study results. Third, our study only focused on companies with oncology products, as oncology has traditionally been the most common condition targeted by registered EA programs.⁴ However, we cannot make claims about non-oncology drug companies. Fourth,

because of our data sources and the inclusion of private companies in the sample, market capitalization data were not available for all companies, we thus used company revenue instead. Finally, we equated a publicly available EA policy with a policy being posted on a company's website; it is possible that a company made its policy public through some other process. In such rare cases, we would have incorrectly considered that the company was noncompliant due to the lack of policy on its website.

CONCLUSION

Despite legal requirements, most applicable oncology drug companies do not have public EA policies as required. Those policies that are publicly available, are missing important information. These findings suggest there are substantial informational gaps for patients and physicians on how to request nontrial pre-approval access to experimental oncology drugs from certain pharmaceutical companies. These gaps are likely particularly acute for products sponsored by smaller and newer companies. There is significant room for improvement in helping patients and doctors understand and timely navigate access pathways for experimental interventions for serious and life-threatening oncology conditions from individual companies.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

S.K., S.C., J.R., and J.M. wrote the manuscript. S.K. and S.C. designed the research. S.K. performed the research and analyzed the data, and contributed new analytical tools.

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1. Reagan-Udall Foundation for the Food and Drug Administration. *Expanded Access Navigator* <<https://navigator.reaganudall.org/>>.
2. Jung, E., Zettler, P.J. & Kesselheim, A.S. Prevalence of publicly available expanded access policies. *Clin. Pharmacol. Ther* **104**, 1016–1021 (2018).
3. Woollett, G. & Jackson, J. *Manufacturer's Compassionate Use Policies: Companies with Posted Policies More Than Doubled Since September 2016* <<https://avalere.com/insights/manufacturers-compassionate-use-policies-companies-with-posted-policies-more-than-doubled-since-september-2016>> (2017).
4. Miller, J.E., Ross, J.S., Moch, K.I. & Caplan, A.L. Characterizing expanded access and compassionate use programs for experimental drugs. *BMC Res. Notes* **10**, 1–4 (2017).
5. U.S. Food & Drug Administration. *Project Facilitate* <<https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate>>.
6. Pharma Intelligence. *Pharmaprojects* <<https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/pharmaprojects>>. Accessed May 15, 2020.
7. Samples of Expanded Access Policies | Expanded Access Navigator <<https://navigator.reaganudall.org/resources/samples-expanded-access-policies>>. Accessed June 23, 2020.
8. Anderson, M.L., Chiswell, K., Peterson, E.D., Tasneem, A., Topping, J. & Califf, R.M. Compliance with results reporting at ClinicalTrials.gov. *N. Engl. J. Med.* **372**, 1031–1039 (2015).
9. Miller, J.E., Korn, D. & Ross, J.S. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. *BMJ Open* **5**, e009758 (2015).
10. Zarin, D.A., Tse, T., Williams, R.J., Califf, R.M. & Ide, N.C. The ClinicalTrials.gov results database—update and key issues. *N. Engl. J. Med.* **364**, 852–860 (2011).
11. Mack, G.S. Expanded access rules pose quandary for drug developers. *Nat. Biotechnol.* **27**, 871–872 (2009).
12. Darrow, J.J., Sarpatwari, A., Avorn, J. & Kesselheim, A.S. Practical, legal, and ethical issues in expanded access to investigational drugs. *N. Engl. J. Med.* **372**, 279 (2015).
13. Nightingale, S.L. FDA Expanded Access Programs for Experimental Medicines. *JAMA* **314**, 1296 (2015).
14. Kearns, L. et al. Gene therapy companies have an ethical obligation to develop expanded access policies. *Mol. Ther.* **29**, 1367–1369 (2021).
15. Caplan, A.L. & Ray, A. The ethical challenges of compassionate use. *JAMA* **315**, 979–980 (2016).
16. Feit, N.Z. et al. Use, safety, and efficacy of single-patient use of the US Food and Drug Administration expanded access program. *JAMA Oncol.* **5**, 570 (2019).
17. Jarow, J.P. & Moscicki, R. Impact of expanded access on FDA regulatory action and product labeling. *Ther. Innov. Regul. Sci.* **51**, 787–789 (2017).
18. Polak, T.B., van Rosmalen, J. & Uyl-de Groot, C.A. Expanded Access as a source of real-world data: An overview of FDA and EMA approvals. *Br. J. Clin. Pharmacol.* **86**, 1819–1826 (2020).
19. Tibbets, J. & Varond, A. Expanded Access Policy Disclosure and Federal Right-to-Try Law. June 7, 2018.