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A survey of pediatric hematologists/oncologists' perspectives on single patient Expanded Access and Right to Try

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Abstract

Introduction: Physicians in the United States play an essential role guiding patients through single patient pre-approval access (PAA) to investigational medical products via either the Food and Drug Administration (FDA)'s Expanded Access (EA) or the federal Right To Try (RTT) pathways. In this study, we sought to better understand pediatric hematologist/oncologists' attitudes about seeking PAA, on behalf of single patients, to investigational drugs outside of clinical trials.

Methods: A cross-sectional survey was developed and sent to pediatric hematologist/oncologists via St. Baldrick's Foundation's email distribution list.

Results: Of 73 respondents (10.1% of those who received the survey), 56 met eligibility criteria and are included in the analysis. Over 80% ($n = 46$) had prior experience with single patient PAA. Respondents were most concerned about the unknown risks and benefits of investigational drugs and financial implications of PAA for patients. One hundred percent and 91.1% of respondents indicated a willingness to support patients through EA and RTT pathways, respectively. When asked about their most recent experience with PAA, 40 out of 46 indicated that they used the FDA's EA pathway to seek PAA and 4 out of 46 indicated that they used the RTT pathway. Of 44 respondents who had used the EA or RTT pathway, 43 indicated that the biotechnology or pharmaceutical company they solicited granted access to the requested product.

Conclusion: Survey results support other findings suggesting a need for additional physician support and education about PAA and that physicians may have unequal access to information about investigational drugs and concerns about financial implications of PAA for their patients.

Keywords

Expanded Access, Right to Try, investigational drug, clinical trials, rare disease, drug development, life-threatening disease, pediatric hematology and pediatric oncology

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Introduction

The primary way patients access investigational drugs is by enrolling in research, which preserves the integrity of drug development and supports evidence-based medicine;[1] however, not all patients who wish to try a particular experimental product can participate in clinical trials. Trials may be full, patients may not meet eligibility criteria, or financial or logistical impediments may prevent participation.[2] When a patient has no US Food and Drug Administration (FDA)-approved treatment options but cannot participate in a trial, there is the possibility of pre-approval access (PAA), which historically has been

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referred to as "compassionate use."[3] With PAA, the primary purpose is not the creation of generalizable knowledge but rather the diagnosis, monitoring, or treatment of a patient's disease or condition. Different countries have PAA programs of a variety of names and descriptions.[4] The United States has two pathways for accessing PAA: the FDA's long-standing Expanded Access (EA) pathway and the federal Right to Try (RTT) pathway, signed into law in May 2018.[8] Both of these pathways can accommodate single patients, the focus of this study. EA can also accommodate groups of patients,[6,7] but RTT cannot.[5] For both single patient EA and RTT, a physician must facilitate the request.[3,9]

To qualify for EA, patients must have a serious or immediately life-threatening disease or condition for which there are no alternative options, including marketed therapies or clinical trial participation.[1,6,9] On behalf of their patients, physicians ask the sponsors developing an investigational product—usually pharmaceutical companies—for access to that product outside of a clinical trial. Companies may decline these requests,[1] but if they agree to provide the product, a protocol devised by the physician (often with company help) is sent to the FDA for review.[10] The FDA and the sponsor must ensure that providing EA will not interfere with clinical trials and that potential benefits of the treatment for that patient justify potential risks.[3,10] EA requests must additionally be reviewed by a designated member of an Institutional Review Board (IRB) unless the request meets specific emergency criteria.[11,12]

To use the federal RTT pathway, patients must have a life-threatening disease or condition. Patients must have exhausted approved options and be unable to participate in a clinical trial involving the desired investigational product. The product must have completed a Phase-I trial, be in active clinical development, and not subject to a clinical hold by the FDA. Neither FDA nor IRB approval is required, but patients must provide the treating physician with written informed consent. As in EA, patient requests for access via RTT must be channeled through a physician and may be declined by the sponsor.[5,9,13]

Despite the critical role physicians play in single patient PAA, relatively little is known about physician knowledge of and familiarity with this option or about what factors influence a physician's decision to seek, or not seek, PAA, via either EA or RTT, on behalf of a patient.[14–16] Moerdler et al.[14] surveyed US pediatric oncologists in the United States to assess their awareness and utilization of EA but did not include questions about RTT; it was conducted in the first half of 2016 (CRC personal communication with Dr. Lindy Zhang, 4 October 2019), over a year before the federal RTT act became law.

In this study, we surveyed US pediatric hematologist/oncologists about their experiences with and perspectives on single patient PAA approximately 1 year after passage of the federal RTT law, which created a new pathway for and raised awareness about potential options for accessing investigational drugs. As most oncology drugs are tested in adults before pediatric trials are conducted[17] and pediatric hematology/oncology involves serious and life-threatening diseases, PAA is particularly pertinent to this therapeutic area. We sought to identify and better understand factors that influence physician willingness or lack of willingness to apply for EA and/or RTT. We also wanted to learn more about the nature and outcome of their most recent PAA requests. Better understanding of physician attitudes and experiences relating to single patient PAA may support data-driven improvements to the process by which patients with serious or life-threatening conditions access investigational drugs outside of clinical trials.

Methods

Survey design

This study was approved as exempt by NYU Grossman School of Medicine (SOM)'s IRB (#s18-01604). An online Qualtrics survey was developed after an analysis of the background PAA literature as well as previous surveys that were related in purpose and/or target population.[14] It was revised and edited in a collaborative and iterative fashion incorporating feedback from members of the NYU Grossman School of Medicine Working Group on Compassionate Use and Preapproval Access, a researcher with expertise in survey development, and five pediatric hematologist/oncologists who completed a draft survey and subsequently answered questions by telephone about the survey's understandability and readability, completion time, relevance of the questions, and any other suggestions for improvement.

The survey (see Supplemental Materials) included 57 questions: 1 open-ended, 3 numerical text entry, 53 multiple choice (of which 32 used a Likert-type scale, 1 allowed multiple answers, 2 allowed a free text entry option, and 2 allowed multiple answers as well as a free text entry option) across 3 different sections. In the "Description of you and your practice" section, the survey sought demographic data on the physicians, as well as information about their clinical practices. The "Your perspectives on single patient access to investigational drugs, including biologics, outside of clinical trial settings" section included questions about factors that influenced the decision to pursue PAA on behalf of patients. The "Your experience with single patient access to investigational drugs, including biologics, outside of a clinical setting" section asked respondents whether they had direct experience with EA or RTT. If so, it asked how they identified the investigational drug of interest, which pathway they utilized, whether the company granted access, whether the FDA reviewed and/or allowed the request to proceed, whether the IRB reviewed and/or allowed the request to proceed, whether the patient was treated with the investigational drug, and, if so, whether such use was viewed as beneficial to the

patient or their family, and whether and from whom physicians received support or assistance with the request.

Recruitment

St. Baldrick's Foundation, a not-for-profit organization dedicated to raising and distributing funds for pediatric cancer research, has a contacts database, which includes pediatric cancer researchers, St. Baldrick's grantees, reviewers, and advisers. This email list of researchers was used as a convenience sample for this exploratory quantitative study. St. Baldrick's emailed an invitation to participate in the survey to 724 individuals in its database: individuals known not to be pediatric hematologist/oncologists by St. Baldrick's database managers were excluded from the email. Recipients could forward the invitation to other US-based pediatric hematologist/oncologists. Email invitations/reminders were sent on April 4, 11, 18, May 23, and June 7, and the survey closed on June 21, 2019. As an incentive to participate, those who completed the survey could enter a raffle to win one of five $100 gift cards.

Data collection

Survey respondents who were not medical doctors, did not specialize in pediatric hematology/oncology, and/or did not spend some of their professional time in patient care were excluded from the study (the survey ended if these eligibility criteria were not met). Participants who met the eligibility criteria indicated consent to participate by submitting the survey.

Partially completed surveys (in which some questions had been skipped) were included in the analysis. A separate REDcap survey captured names and contact information of those who wished to enter the lottery and/or be contacted for follow-up.

Data analysis

Survey data were exported from Qualtrics into Excel and analyzed using *R* version 3.4.3. Two of the authors were involved with tabulating results for quality control. Descriptive statistics were computed for each of the individual survey questions. Categorical variables were reported as frequency counts and percentages, and continuous variables were summarized using appropriate measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range). Free-text responses were summarized to protect patient and/or physician anonymity; formal coding was not performed because of the limited amount of qualitative data. When appropriate, questions of interest to the main survey objectives were stratified by either demographic variables or responses to other survey questions, and hypothesis testing was performed to compare ratios using a two-sample chi-square test for equality of proportions with continuity correction.

Table 1. Description of respondents meeting inclusion criteria.

	Number (percentage)
Career stage	
Board certified in pediatric hematology/oncology*	51 (91.1%)
Board eligible—pediatric hematology/oncology	4 (7.1%)
Fellow in pediatric hematology/oncology; not yet board eligible	1 (1.8%)
Professional time spent on clinical care of patients	
1%–25%	18 (32.1%)
26%–50%	15 (26.8%)
51%–75%	12 (21.4%)
76%–100%	11 (19.6%)
Clinical practice affiliated with academic medical center	
Yes	48 (85.7%)
No	8 (14.3%)
Description of medical center affiliated with practice#	
Focused on care of children only	32
Focused on care of adults and children	21
Focused on cancer care	17
Provides care in many therapeutic areas	23
Not affiliated with medical center	1
New hematology/oncology patients seen per year at clinical practice	
1–50	5 (8.9%)
51–100	14 (25.0%)
101–250	16 (28.6%)
250–500	15 (26.8%)
501–1000	4 (7.1%)
Over 1000	1 (1.8%)
Not answered	1 (1.8%)
Number of patients for whom have sought single patient pre-approval non-trial access	
None	10 (17.9%)
One	9 (16.1%)
2–5	27 (48.2%)
6–10	5 (8.9%)
10 or more	5 (8.9%)

*Median 17.5 years board certified (range: 1–39 years).
#Percentage not provided as more than one answer could be selected.

Results

Respondents' self-reported characteristics

There were 73 responses to the cross-sectional, online survey (10.1% response rate, $n = 724$). Responses from 56 pediatric hematologist/oncologists who met eligibility criteria were included in the analysis. Their self-reported characteristics are described in Table 1. Over 80% of

Table 2. Perspectives on alternative pathways for single patient access to investigational drugs, outside of clinical trials.

	. . . the FDA's EA program		. . . the federal RTT pathway		p value*
	SA/A	D/SD	SA/A	D/SD	
If my patient meets eligibility requirements, I would consider applying, on his/her behalf, for access to an investigational drug through . . .	56	0	51	5	0.067
I am familiar with the process by which to seek an investigational drug for my patient, through . . .	38	18	14	42	<0.001
My clinical practice/ colleagues would be supportive of my choice to seek access to an investigational drug or biologic on behalf of a patient through . . .	53	3	47	9	0.127

SA: strongly agree; A: agree; D: disagree; SD: strongly disagree.
*A two-sample chi-square test for equality of proportions with continuity correction was performed to calculate *p* values.

respondents (46/56) reported prior experience with single patient PAA. Almost 9% of respondents (5/56) reported seeking such access for 10 or more patients. However, almost 18% (10/56) had not had prior experience with PAA and approximately 16% (9/56) had sought such access only for one patient. Sub-group analyses revealed that a respondent's current clinical practice being affiliated with an academic medical center (48/56; 85.7%) versus not (8/56; 14.3%) did not significantly influence the number of patients for whom the respondent had sought PAA ($p < 0.327$). Among the 19 clinicians who sought access for 0–1 patients, 18 (95%) were affiliated with an academic medical center, while among the 10 clinicians who sought access for six or more patients, 8 (80%) were affiliated with an academic medical center ($p < 0.55$). Similarly, practice size, defined here as seeing either up to 250 new hematology/oncology patients per year (35/56), or 250 or greater (21/56), did not significantly influence the number of patients for whom PAA was sought ($p < 0.53$).

Respondents' perspectives on PAA

One hundred percent of respondents (56/56) indicated willingness to support a patient through single patient EA, while 91.1% of respondents (51/56) indicated willingness to support a patient through RTT ($p < 0.067$, Table 2). Thirty-eight of 56 respondents (67.9%) strongly agreed or agreed that they were familiar with the EA process, but only 25.0% (14/56) strongly agreed or agreed that they were familiar with the RTT process (Table 2).

The survey sought to ascertain the relative importance of several factors in physician decision-making about seeking PAA, via either pathway, on behalf of a patient in general (see Table 3). Almost 84% of respondents (47/56) indicated that the unknown benefit/risk profile of the investigational drug was a very important or moderately important factor in making decisions to seek PAA (see Table 3(b)). Forty-three of 56 respondents (76.8%) indicated that "the cost of the drug may not be covered by my patient's insurance (or because of other financial reasons impacting the patient or their family)" was a very important or moderately important factor in their (the respondent's) decision to seek PAA (Table 3(b)). One respondent commented by text entry that the cost of acquiring a specific investigational drug for EA was $100,000; neither the drug cost nor the pharmacy preparation or drug administration was covered by the patient's insurance. Factors relating to lack of knowledge—specifically about which investigational drugs might be available for PAA, about the process for seeking PAA, and about how to use investigational drugs outside clinical trials—were endorsed as very or moderately important factors in decisions to seek PAA by 41.1% (23/56), 37.5% (21/56), and 39.3% (22/56) of respondents, respectively (Table 3(b)). In contrast, concerns about legal liability and the lack of compensation for time spent were rated as very important or moderately important factors by only 14.3% (8/56) and 5.4% (3/56) of respondents, respectively (Table 3(b)).

Respondents' experiences with PAA

Respondents experienced with PAA were asked about the importance of various factors specific to *their most recent* experience with PAA. The factors endorsed as most important included no approved therapies available to treat the patient, the patient had exhausted all approved therapies, and that the investigational drug was the best therapeutic option for that patient (Supplemental Table S1). When asked how the investigational drug/biologic for their most recent PAA request was identified, some indicated that a colleague or family member suggested it (19/46 and 3/46 respondents, respectively). Others indicated that they identified it themselves, through PubMed (8/46), ClinicalTrials.gov (1/46), or by other mechanisms (14 of 15 free text entries described ways the physician learned of the drug). Notably, 11 respondents wrote that they (or their institutions) had prior experiences with or knowledge about the investigational drug; for example, one stated that they were the principal investigator on a trial of the product; another stated that their institution had an ongoing adult trial with

Table 3. Respondents' perspectives on single patient access to investigational drugs outside of clinical trial settings.

A. How often do the following scenarios occur?	VO	O	S	R	*p* value	Weighted score
Patient exhausts all approved therapies	12 (21.4%)	25 (44.6%)	18 (32.1%)	1 (1.8%)	0.001	2.9
No approved therapies available to treat the patient	11 (19.6%)	23 (41.1%)	18 (32.1%)	4 (7.1%)	0.038	2.7
Patient unable to participate in clinical trial for desired investigational drug because . . .						
. . . he/she does not meet inclusion/exclusion criteria	6 (10.7%)	19 (33.9%)	26 (46.4%)	5 (8.9%)	0.345	2.5
. . . there were no spots and/or the trial was no longer enrolling	6 (10.7%)	16 (28.6%)	26 (46.4%)	8 (14.3%)	0.038	2.4
. . . because of logistical barriers	3 (5.4%)	11 (19.6%)	31 (55.4%)	11 (19.6%)	<0.001	2.1
. . . because of financial barriers	2 (3.6%)	7 (12.5%)	17 (30.4%)	30 (53.6%)	<0.001	1.7
Patient not interested in participating in clinical trial(s)	0 (0%)	6 (10.7%)	28 (50%)	22 (39.3%)	<0.001	1.7
B. Factors important in decision(s) to seek single patient, non-trial pre-approval access to an investigational drug	**VIF**	**MIF**	**SF**	**NF**	***p* value**	**Weighted score**
The risks and/or benefits of investigational drug are not known.	16 (28.6%)	31 (55.4%)	8 (14.3%)	1 (1.8%)	<0.001	3.1
The cost of the drug may not be covered by my patient's insurance (or because of other financial reasons impacting the patient or their family).	20 (35.7%)	23 (41.1%)	8 (14.3%)	5 (8.9%)	<0.001	3.0
It is difficult for me to identify investigational drugs/biologics that have potential to help my patient.	11 (19.6%)	12 (21.4%)	16 (28.6%)	17 (30.4%)	0.089	2.3
I do not have enough information about how to seek non-trial pre-approval access.	9 (16.1%)	12 (21.4%)	19 (33.9%)	16 (28.6%)	0.014	2.3
I do not have enough information to use investigational drugs outside a clinical trial.	3 (5.4%)	19 (33.9%)	18 (32.1%)	16 (28.6%)	0.038	2.2
I do not have time to support single patient, non-trial pre-approval access requests.	5 (8.9%)	11 (19.6%)	23 (41.1%)	17 (30.4%)	<0.001	2.1
It is difficult to get approval for single patient pre-approval non-trial access to investigational drugs from my institution.	3 (5.4%)	12 (21.4%)	23 (41.1%)	18 (32.1%)	<0.001	2.0
I have concerns about legal liability.	1 (1.8%)	7 (12.5%)	18 (32.1%)	30 (53.6%)	<0.001	1.6
I may not be paid for my time and effort (or because of other financial reasons impacting me/my instituion/my practice).	0 (0%)	3 (5.4%)	8 (14.3%)	45 (80.4%)	<0.001	1.3

VO: very often; O: often; S: sometimes; R: rarely; VIF: very important factor; MIF: moderately important factor; SF: slight factor; NF: not a factor.
p values were calculated using a two-sample chi-square test for equality of proportions with continuity correction and compared responses VO or O versus S or R.
To create weighted scores, each response was multiplied by a weight factor to adjust for importance (4 for VO or VIF; 3 for O or MIF; 2 for S or SF; 1 for R or NF). These adjusted factors were totaled. The total was divided by the number of responses (56).

the drug; another wrote that they were familiar with the agent from their own clinical research experience.

Of 46 respondents with prior PAA experience, 40 indicated they used the EA pathway, 4 RTT, and 2 did not specify/answer (Table 4). Of these respondents, many indicated they received help from various sources: administrative staff within their practice (32/46); representative from manufacturer/developer of investigational drug or biologic (31/46); IRB member or staff at their institution (27/46); FDA representative (7/46); social worker or patient advocate within their practice (5/46); and patient advocate outside their practice (1/46). Write-in responses to this question included: pharmacy staff (2/46), clinical colleagues (3/46), and family of the patient (1/46).

Of 44 respondents who used either the EA or RTT pathway, only 1 (2.3%) indicated that the pharmaceutical company did not grant their request, and 39 (88.6%) indicated that the patient or their family benefited from the experience (Table 4). Forty-one respondents answered a separate multiple-choice question asking about the nature of this benefit, in which more than one choice could be selected. Of the 41 responses, 33 indicated that the family had psychological benefit (e.g. focus on hope); 23 indicated the patient had psychological benefit (e.g. focus on hope); 18 indicated the patient had improvement in overall survival; 17 indicated the patient had improved quality of life. Eleven respondents to this question indicated there were "other" benefits and provided free text entries: six noted

Table 4. Description of the nature and outcome of respondents' most recent experience with a single patient pre-approval non-trial access request.

Pathway used	Number	Did the pharma or biotech grant access?		Did the FDA review the request?		Did the FDA allow the request to proceed?			Did you submit the request to an IRB?		Did the IRB approve or concur with the request?			Did you treat the patient with the investigational drug or biologic?		Do you believe patient or family benefited from this experience?	
		Yes	No	Yes	No	Yes	No	N/A	Yes	No	Yes	No	N/A	Yes	No	Yes	No
FDA EA	40	39	1	35	4	34	0	6	37	2	37	0	2	37	2	36	4
RTT	4	4	0	1	2	1	0	2	2	2	2	0	2	3	1	3	1
Not specified	2	0	1	0	1	0	0	1	0	1	0	0	1	1	0	2	0
Total#	46	43	2	36	7	35	0	9	39	5	39	0	5	41	3	41	5

FDA: Food and Drug Administration; IRB: Institutional Review Board; EA: Expanded Access; RTT: Right to Try.
#The 46 respondents did not each answer all the questions about the nature and outcome of their most recent PAA experience.

clinical benefits to patient; three noted benefits to the family of the patient; one noted that they/their institution learned from the experience.

A text-entry question at the end of the survey asked if there was anything else respondents would like to share about their experience(s) with PAA. Three respondents stressed the importance of PAA; one noted that the pathways "provide real hope" to patients and families and that patients can gain "real quality of life." Another noted that PAA can be "a way to gain access to appropriate specifically targeted agents, drugs approved in Europe, but not the US, or drugs on the cusp of FDA approval." Five noted the time-consuming and/or labor-intensive nature of PAA; one wrote that it involved a lot of unpaid time for the physician. Two respondents noted positive experiences with the FDA; one stated strong opposition to the RTT legislation. One noted that their division has staff dedicated to facilitating the PAA process. Three wrote about the difficulty their patients have in getting access to clinical trials—due to a "paucity" of available trials, age-related eligibility criteria, and lack of liquid formulations and/or appropriate dosing for pediatric patients. One respondent without prior PAA experience noted that the process is not clear; another noted that they had only tried to access drugs through companies' patient assistance programs, a response which likely refers to trying to obtain free access to approved drugs, which is not PAA. One respondent with prior PAA experience noted that they do not typically "go this route," but instead utilize the "insurance and appeals process"; this respondent may have been referring to off-label use of approved drugs rather than PAA. Indeed, the FDA has acknowledged that it sometimes receives "PAA" requests concerning off-label uses of approved drugs, even though FDA involvement is not required for uses of approved medical products for indications beyond those for which they were approved.[18]

Discussion

To seek PAA, patients must have support from their physicians. Of the pediatric hematologists/oncologists who responded to this survey, 100% (56/56) and 91.1% (51/56) indicated willingness to utilize the single patient EA and RTT pathways, respectively, to access unapproved drugs outside of clinical trials. The strong support for both pathways is a striking finding, given the intense national debate around RTT;[19–22] however, this result must be interpreted in the context of 32.1% (18/56) and 75% (42/56) of respondents indicating lack of familiarity with the EA and RTT processes, respectively. Indeed, in a recently published qualitative interview study, oncologists expressed concerns about RTT, including lack of adequate oversight and patient safety.[23] Interestingly, oncology was the only clinical specialty to formally take a position with regard to the federal RTT pathway before it became law. The American Society of Clinical Oncology

released a statement opposing the legislation;[24] the American Society for Pediatric Hematology/Oncology did not take a position.

At the time, this survey was administered, there had been only two publicized uses of the federal RTT pathway reported in the literature and media.[25,26] As such, it is unexpected that four respondents in a small sample indicated they had sought access to investigational drugs via the RTT pathway. In one of these cases, the patient passed away before treatment could begin. Another respondent reported that the FDA allowed an RTT request to proceed. As FDA review is not required in the RTT pathway, this is an intriguing result and raises the possibility of reporting error. However, in one of the publicized cases of RTT, the FDA was notified of the request prior to use, exceeding the federal legal requirements for reliance on the pathway.[27]

It is noteworthy that only one out of the 44 respondents who described their most recent PAA experience indicated that the company did not grant access. While sponsors can and do deny pre-approval non-trial access requests,[2,28–30] companies may be more likely to grant requests for investigational products in pediatric hematology/oncology than in other therapeutic areas. Data from three large pharmaceutical companies, Novartis, Janssen, and Pfizer, indicate that they have granted more than 90% of overall EA requests received.[31–33] Reporting bias is also possible: respondents may have preferentially remembered recent PAA experiences in which companies granted requests for investigational drugs. That 31/44 respondents indicated that a representative from a company helped them with the PAA process suggests companies are directing resources to manage, respond to, and assist with PAA requests. It is interesting that only 7/44 respondents reported receiving assistance from the FDA, despite the fact that the agency has long had staff available for this purpose. This may change, as the FDA launched a pilot program, Project Facilitate, to assist oncologists with single patient EA requests in June 2019.[32] This survey closed just a few weeks after the launch of Project Facilitate.

Our results suggest that more focus is needed on equality of opportunity for PAA. Some physicians reported supporting several patients through PAA, while others reported no prior experiences; thus patient access to PAA is variable by physician. When asked how they learned about the investigational drug of interest for their most recent PAA experience, many respondents indicated they had personal experience with or knowledge about the investigational product, such as direct or institutional involvement with the clinical trial. This suggests that physicians rely on their prior knowledge or proximity to research, rather than utilizing public databases and resources that may provide a more comprehensive understanding of what investigational agents may be of use and are available.[34,35]

Furthermore, many respondents indicated that the financial implications for the patient are a major factor in considering whether to seek PAA. This aligns with findings from previous research.[15,36] In a 2018 survey of physicians, "getting reimbursed from the patient or insurance company for the drug, IRB fee, and other costs incurred" was most frequently rated the most difficult step in the EA process.[15] Although it is believed that many companies do not charge for their unapproved products used via PAA, further research is needed to understand how often and whether companies charge for PAA and, if so, how much. US regulations specify that charging for investigational products provided via EA or RTT must be limited to direct costs.[5] Companies must submit justification for any charges for EA to the FDA; however, there is confusion about what entity, if any, will oversee this rule for RTT.[5,37] Respondents self-reported that uncompensated effort was generally not a factor in their decision whether to seek PAA. It is possible that this underestimates the importance of unreimbursed physician effort and time. Indeed, five respondents made references to the time and/or labor intensity of PAA in their free text entry comments.

Results from this survey support other research suggesting a need for additional physician support and education on PAA.[14,15,23] Eighteen of 56 respondents (32.1%) indicated lack of familiarity with the EA process, and 42/56 (75%) indicated lack of familiarity with the RTT process (Table 2). This is somewhat surprising, given that over 80% of the respondents self-reported prior experience with PAA. Data collected about the physician's most recent PAA experience raise some questions about reporting accuracy. It is not clear that some of the self-reported EA cases fit the technical definitions of EA; for example, there were 39 self-reported EA cases where the sponsor agreed to provide product and 37 cases in which the patient was treated with the investigational drug, yet 4 of these cases were reported as not to have been reviewed by the FDA. Given the series of gatekeepers in EA—physician, the sponsor, the FDA, and finally the IRB—these discrepancies demonstrate incorrect or incomplete understanding of EA by physicians surveyed. The survey format did not allow further probing. But confusion about terminology is a well-known problem in this area,[4] and, as indicated above, acquiring approved drugs for off-label use at no cost is sometimes (imprecisely) considered EA.[18] Our findings also align with interview data from a recently published qualitative study, which found that oncologists from a major cancer center have misperceptions and confusions regarding RTT.[23]

Overall, results from this survey support Moerdler et al.'s recommendation that "pediatric oncologists may benefit from educational resources and support to ensure children with cancer have equal access to investigational agents and care."[14] Recently published qualitative research also indicates that oncologists desire additional administrative support and education on PAA processes.[23] As previously noted, the FDA's pilot program, Project Facilitate,

aims to assist oncologists with single patient EA.[32] Other resources for physicians and patients include a navigator service for EA provided by Kids V Cancer, a patient advocacy group focused on pediatric oncology.[35] The Reagan-Udall Foundation's Expanded Access Navigator provides information and resources to physicians and patients considering EA.[34] Once investigational drugs enter Phase-2 testing, sponsors are required to post information about the potential availability of EA on the *ClinicalTrials.gov* database.[30] Furthermore, the 21st Century Cures Act requires sponsors to publicly post their EA policies and a means of contact for requests and questions once agents enter Phase 2 clinical trials. Although there are many available EA resources, future studies should investigate the effectiveness of different mechanisms to inform physicians about EA and its associated processes. It is unclear which organization(s) should or might serve to educate physicians about RTT.

Study limitations

Although our survey response rate was low at 10.1%, it is comparable to the response rate for other surveys of pediatric hematologists/oncologists.[14] Also, it is difficult to determine the true response rate as the St. Baldrick's distribution list included some individuals who were not practicing pediatric hematologists/oncologists, despite the intention to send invitations only to this specific group. Because of the low number of responses ($n = 56$) that met inclusion criteria, our results may only be suggestive of trends and are not generalizable to the population of pediatric hematologists/oncologists. Also, all the physicians' responses, including the descriptions of their most recent PAA experiences, are self-reported from memory and thus subject to recall bias and distortion. Although we included information about EA and RTT at the beginning of the survey, some respondents may have confused single-patient PAA with off-label use that is not reimbursed by insurers or with the provision of approved drugs via patient assistance programs.

Conclusion

An online survey of pediatric hematologists/oncologists found widespread willingness to seek PAA for single patients, through either of the two pathways currently available in the United States. The results also support other research suggesting a need for additional physician support and education about EA and RTT.[14,23] Future research should be investigating the efficacy of various mechanisms to improve equity for PAA opportunities, as justice concerns arise when information about investigational drugs is not available to all physicians and when physicians are concerned about financial implications of PAA for their patients. Other commentators have also called for increased efforts to educate physicians about PAA. Better understanding of physician attitudes and experiences with EA and RTT, fostered by the insights from this study, will allow targeted improvements to the process by which physicians can seek access to investigational drugs outside of clinical trials when their patients have no other options.

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Authorship

All of the co-authors meet the criteria for co-authorship, including making a substantial contribution to the concept or design of the work; or acquisition, analysis, or interpretation of data, drafted, and/or revised the manuscript critically for important intellectual content, approved the submitted version, and each author has participated sufficiently to take public responsibility for appropriate portions of the content.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.B.-H. serves as an unpaid chair and an unpaid committee member for the NYU Compassionate Use Advisory Committees (CompAC), external panels of medical experts, bioethicists, and patient representatives formed by NYU Grossman School of Medicine in collaboration with Janssen Pharmaceuticals to advise Janssen about requests for compassionate use of its investigational medicines. The university receives administrative funding from Janssen to facilitate the CompAC program. At the time of this study, she was an associate fellow of the GE2P2 Global Foundation and a member of its Independent Bioethics Advisory Committee (IBAC), which provide bioethical consultative services to commercial and other biopharma organizations on clinical trials, expanded access programs for investigational medicines and therapies, and in other areas. She has accepted speaking fees and/or travel expenses from the American Association for Cancer Research; Amyloidosis Research Consortium; Biogen; European Organization for the Research and Treatment of Cancer; Johnson & Johnson; the Reagan-Udall Foundation for the FDA; and the US FDA. She receives payment for work on data safety monitoring committees, one for a clinical trial sponsored by the National Eye Institute and one run by NYU Langone Health. She has served as an unpaid advisor to numerous

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The NYU Grossman School of Medicine IRB approved this study as exempt (#18-01604) and permitted a waiver of documentation of consent. As the survey was conducted online, it was not possible to obtain written informed consent. Instead, subjects indicated their agreement to participate in the study through the process of voluntary completion and submission of the survey.

Availability of data and materials

Please contact the corresponding author to request information.

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Supplemental material

Supplemental material for this article is available online.

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