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Prescribing unproven cancer drugs: physician perspectives on expanded access and right to try

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ABSTRACT

Background: For gravely ill patients who have no treatment options and who are ineligible for clinical trials, the US Food and Drug Administration (FDA) established the Expanded Access Program (EAP). Motivated by efforts to weaken FDA regulation and sold as providing greater access to experimental drugs, the federal Right to Try Act (RTT) was passed in 2017. It reduces FDA oversight by not requiring physicians to report safety data and foregoes approval of protocols by local institutional review boards.

Methods: This study explored the views of 17 neuro-oncologists from 15 different academic medical centers with varying experience with EAP and RTT using convenience sampling. We conducted semi-structured interviews and qualitative analysis to identify emerging themes.

Results: Most oncologists were confused between the two pathways, had little familiarity with RTT, and had little knowledge about experimental medicine available through either pathway. Oncologists reported a preference of enrolling patients in clinical trials over off-trial preapproval pathways with scant data. As a result, oncologists revealed concerns over properly evaluating risks for their patients.

Conclusion: Our findings suggest that neuro-oncologists need better resources and clearer mechanisms at their institutions to help navigate EAP and RTT in order to counsel patients interested in experimental medicine.

KEYWORDS: Expanded Access, Right to Try, FDA, ethics, neuro-oncology, Compassionate Use

† Zubin Master and Christopher Thomas Scott are Co-senior authors.

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I. INTRODUCTION

I.A. Non-trial preapproval access: Expanded Access, Compassionate Use and Right to Try

For gravely ill patients who have no viable treatment options and who are ineligible to participate in clinical trials, the US Food and Drug Administration (FDA) established the Expanded Access Programs (EAPs) in 1987.^{1,2} There are three types of EAPs: for single patients (also called ‘Compassionate Use’), intermediate size populations, and treatment group populations. Single patient EAP requests can be made to the FDA for emergency and non-emergent situations with different approval times and mechanisms. In the context of a single patient EAP, unapproved products can be given to patients at various stages of clinical development. From a single major cancer center, over three-quarters of single patient EAP protocols were drugs being tested in phase 2 or 3 trials, but nearly 20 per cent were tested in phase 1 safety trials.³

Over the years, the FDA has streamlined the process to improve access to experimental cancer medicines outside of a clinical trial, in part by establishing *Project Facilitate*. This project helps streamline the administrative elements of EAPs by providing a call service and helping physicians complete the application.⁴ Additional improvements include requirement of a shorter, 2-page application form, which takes physicians approximately 45 minutes to complete, and review by a single member of the Institutional Review Board (IRB).^{5,6} However, companies are not obligated to provide experimental drugs to patients. Furthermore, companies cannot profit from the provision of drugs, but they may charge for manufacturing and other related costs. The EAP regulations also stipulate reporting requirements to the agency, including adverse events. This regulatory process has been relatively expedient with over 99 per cent of requests being approved, with turnaround approval times between 8 and 26 days, against a target turnaround of 30 days for non-emergency situations. The average time to approval for non-emergent individual patient INDs is 4 days, and emergent IND approval may be granted over the phone within hours.^{7,8} The FDA has also put forward education to physicians, patients, and sponsors.⁹

1 The Food and Drug Administration, *CFR—Code of Federal Regulations Title 21*, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9> (accessed Oct. 19, 2021).

2 The Food and Drug Administration, *Expanded Access Program Report* <https://www.fda.gov/media/119971/download> (accessed July 1, 2021).

3 Feit NZ, Goldman DA, Smith E, Deighan J, Iasonos A, Zivanovic O, Hyman DM. *Use of the US Food and Drug Administration Expanded Access Program*, 5 *JAMA ONCOL.*, 4, 570–572 (2019).

4 The Food and Drug Administration, *Project Facilitate*, <https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate> (accessed July 1, 2021).

5 The Gao Report, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used*, <https://www.gao.gov/assets/gao-17-564.pdf> (accessed July 1, 2021).

6 The Food and Drug Administration, *How to Submit Request Forms*, <https://www.fda.gov/news-events/expanded-access/expanded-access-how-submit-request-forms> (accessed July 1, 2021).

7 Jarow JP, *Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period*, 50 *THER. INNOV. REGUL. SCI.*, 6, 705–709 (2016).

8 Jarow JP, *Ten-year experience for the Center for Drug Evaluation and Research, Part 2: FDA’s Role in Ensuring Patient Safety*, 51 *THER. INNOV. REGUL. SCI.*, 2, 246–9 (2017).

9 Regan Udall Foundation, *Expanded Access Navigator*, <https://navigator.reaganudall.org/> (accessed July 1, 2021).

Despite these largely positive developments, there have been calls for greater reform of FDA pathways, including making Project Facilitate a permanently funded program, addressing barriers for small companies considering offering EAP, and broadening clinical trial eligibility whereby EAP is authorized only when trial participation is infeasible.¹⁰

Gaining non-trial preapproval access from the FDA resulted in the modern form of EAP. In the 1980s, the HIV/AIDS epidemic prompted the FDA to make significant changes to improve patient access to drugs outside of clinical trials and to reduce the time to final FDA authorization. The agency applied an informal standard to individual requests for unapproved drugs until the FDA Modernization Act of 1997 codified what is now known as the Expanded Access Program.¹¹ More recent challenges have sought to provide investigational drugs to terminally ill patients. In the 2000s the Abigail Alliance case involved constitutional claims, and an en banc court ruled that ‘FDA regulation of post-phase I drugs [was] entirely consistent with [the United States’] historical tradition of prohibiting the sale of unsafe drugs’.^{12,13} And a decade ago US Senators Brownback and Inhofe sponsored a bill entitled the ‘Access, Compassion, Care and Ethics for Seriously Ill Patients Act’. This bill also sought to permit marketing of drugs after phase I testing. That bill never made it through committee and as a result never came up for a vote.¹⁴

One federal law did, however, and now the Expanded Access Program is not the only pathway to experimental drugs outside of a clinical trial. Given similar concerns of government overregulation and denial of patient access to experimental medicine, in 2014 the Goldwater Institute, among other think-tanks, put forth policy supporting a patient’s ‘Right-to-Try’ experimental medicine, with a testimonial from an oncologist treating terminally ill patients serving as a centerpiece rationale for the policy.^{15,16} This concept was part of a movement to ensure quicker access to experimental drugs while limiting governmental powers. Goldwater also drafted model Right-to-Try (RTT) legislation that was enacted in 41 states.¹⁷ Generally, state RTT laws permit physicians to request access to investigational drugs on behalf of patients in the absence of FDA and IRB oversight.¹⁸ State laws generally specify that physicians cannot be disciplined for recommending or prescribing investigational medication and that patients can try these products after obtaining informed consent.¹⁹ Heterogeneity among state laws

10 Fernandez-Lynch H and Bateman-House A. *Facilitating both Evidence and Access: Improving FDA’s Accelerated Approval and Expanded Access Pathways: Health Policy Portal*. 48 J.L. MED. ETHICS, 365 (2020).

11 Zach S, *An Examination of the Right to Try Act of 2017 and Industry’s Potential Path Moving Forward*, 92 S. CAL. LAW REV., 331–410 (2019).

12 United States v. Rutherford, 442 U.S. 544 (1979).

13 Allison J Goodman, *Abigail Alliance v Von Eschenbach: Restricting Access to Potentially Lifesaving Drugs since 2007*, 25 J. CONTEMP. HIST. LAW POLICY, 1 (2008).

14 Begg C.B., Kum K.M., Neaton J.D., *Right to Try Laws*. 5 CLIN. TRIALS, 11, 519–520 (2014).

15 Goldwater Institute, *What Is Right to Try?* <http://righttotry.org/about-right-to-try/> (accessed July 1, 2021).

16 Goldwater Institute, *Dr Ebrahim Delpassand’s Official Response to Congressman Pallone and Activist McFayden*, <http://righttotry.org/dr-ebrahim-delpassands-official-response-to-congressman-pallone-and-activist-mcfayden/>, (accessed Mar. 15, 2022).

17 *Id.* at 15.

18 Chapman CR, Eckman J, Bateman-House AS. *Oversight of Right-to-Try and Expanded Access Requests for Off-Trial Access to Investigational Drugs*, 42 ETHICS HUM. RES., 1, 2–13 (2020).

19 Kearns L and Bateman-House A, *Who Stands to Benefit? Right to Try Law Provisions and Implications*, 51 THER. INNOV. REG. SCI., 2, 170–176 (2017).

surround patient eligibility of the ‘terminally ill’ definition and provisions of informed consent. Some state RTT laws permit insurers to deny treatment coverage for harms resulting from the experimental product or make patient who try experimental products ineligible for hospice care.²⁰ Despite the high numbers of state level laws, there has been little uptake of RTT by physicians and their patients.²¹

In 2017, former President Trump signed into law the federal RTT Act.²² Both federal and state RTT laws have come under broad criticism by ethicists, scientists, clinicians, and some patient advocacy organizations and policymakers.^{23–29} Criticism primarily focuses on the increased health and safety risks of patients with many drugs being sought after initial phase 1 safety testing, the lack of regulatory and ethics oversight, few details surrounding the provision of informed consent, limited monitoring and reporting requirements, and the redundancy of the law as EAP already granted patients access to investigational drugs, with near 100 per cent approval by the FDA and rapid turnaround.^{30–33} In addition, two-thirds of early phase drugs fail in later phases of testing, potentially exposing patients to risk and side effects. Despite the legislative focus on the FDA’s shortcomings, it is important to note that decision to provide drugs under RTT, as it is with EAP, is at the discretion of the drug companies. Opponents suggest that RTT does not really grant access to experimental medicines, but rather only guarantees a ‘right to ask’ the drug maker. The manufacturer may deny access, and many advertise that they will not honor RTT requests, for fear that adverse effects may interfere with the success of their application to the FDA.³⁴

In summary, Bateman-House et al. underscore the legal fallout from RTT: ‘(RTT) ignores both the complexity of deciding when access makes sense for desperate patients and the reality that resources are needed to make access possible. Choice without obligation leaves patients where they were before the laws were enacted: begging companies for compassion.’³⁵

20 *Id.* at 18.

21 Barlas S, ‘Right to Try’ Legislation Moving Through Congress but Drug Companies and Some Patient Groups Want Changes, 45 MOD. HEALTHC., 42, 10. (2015).

22 Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina *Right to Try Act of 2017* <https://www.congress.gov/bill/115th-congress/senate-bill/204/text> (accessed July 1, 2021).

23 *Id.* at 18, 20.

24 Hamblin J. *The Disingenuousness of ‘Right to Try’*. THE ATLANTIC, June 2, 2018, at 1.

25 Scott CT, *A ‘Right to Try’ But at What Cost?* <https://blogs.bcm.edu/tag/right-to-try/> (accessed July 1, 2021).

26 Master, Z., Tilburt, J.C., *Physicians’ Ethical and Professional Obligations about Right-to-Try Amidst a Pandemic*. 20 AM. J. BIOETH. 9, 26–28 (2020).

27 Joffe S and Lynch HF, *Federal Right-to-Try Legislation—Threatening the FDA’s Public Health Mission*. 378 N. ENGL. J. MED., 8, 695–697 (2018).

28 Bateman-House A, Robertson CT. *The Federal Right to Try Act of 2017—A Wrong Turn for Access to Investigational Drugs and the Path Forward*, 178 JAMA INTERN. MED. 3, 321–322 (2018).

29 Zettler PJ, Greely HT, *The Strange Allure of State ‘Right-to-Try’ Laws*, 174 JAMA INTERN. MED. 12, 1885–1886 (2014).

30 *Id.* at 18, 20, 23.

31 *Id.* at 26.

32 *Id.* at 27.

33 *Id.* at 28.

34 Gabay M., *A Rapid Review of Right to Try*, 53 HOSP. PHARM. 4, 234–235 (2018).

35 Bateman-House, Kimberly L, Redman B, *Right-to-Try Laws: Hope, Hype and Unintended Consequences*, ANN. INTERN. MED. 163, 796–797 (2015).

I.B. Two Competing Federal Pathways

At present, patients, physicians, and companies are faced with two competing federal pathways, and the publicity surrounding RTT may mean physicians receive more requests for unapproved drugs outside of clinical trials.³⁶ The existence of parallel pathways could result in patient and provider confusion, a need for greater resources, and potential distress for both patients and physicians. Patients and clinicians may be confused about what the RTT law means, given the lack of a positive right obligating a drug company to provide experimental medications to patients. One study of experienced oncologists' attitudes towards off-trial medication showed that several physicians misunderstood and reported that the federal RTT legislation does offer a right for patients to access experimental drugs.³⁷ Clinicians might also have to decide whether patients are *truly* ineligible from enrolling in clinical trials and whether they are siphoning resources from randomized trials.³⁸ While EAP is not without its own shortcomings, including issues of equitable access, most scholars argue that RTT deprives patients of necessary oversight that can reduce harm, and prevents the FDA from using adverse event reporting during the drug approval process.^{39,40}

Given the importance of enhancing clinical research and providing out-of-option patients access to experimental drugs on the basis of compassion, little is known about physician and patient attitudes regarding these pathways. At present, only a handful of studies capture physicians' experiences with EAP and RTT, and a couple of these studies were performed in specific settings.^{41–47} To better understand the views of clinical oncologists, we aimed to explore the attitudes of experienced clinical neuro-oncologists who treat patients with brain tumors towards EAP and RTT. Oncology is one the most prolific areas where physicians obtain experimental products through EAP.⁴⁸ This demand is especially acute in neuro-oncology, where few effective treatments exist, and many patients face end-of-life decisions.⁴⁹ In this study, we interviewed 16 oncologists

36 Lo B, *A Parallel Universe of Clinical Trials*, 379 NEJM., 101–103 (2018).

37 Smith C, Stout J, Adjei AA, Buckner J, Wentworth M, Tilburt J, Master Z. 'I think it's been met with a shrug': Oncologists' Views Toward and Experiences with Right-to-Try, J. NATL. CANCER INST., 1–7 (2020).

38 *Id.* at 26, 31.

39 Fountzilas E, Said R, Tsimberidou AM. *Expanded Access to Investigational Drugs: Balancing Patient Safety with Potential Therapeutic Benefits*. 27 EXPERT OPIN. INVESTIG. DRUGS, 2, 155–162 (2018).

40 Morrison C. *Critics Say 'Right-to-Try' Wrong for Patients*, 36 NAT. BIOTECH., 4, 294–296 (2018).

41 Bunnik EM, Aarts N and van de Vathort S. *Views and Experiences of Physicians in Expanded Access to Investigational Drugs*, 39 CLIN. THER., 8, 96 (2017).

42 Bunnik EM, Aarts N. *What Do Patients with Unmet Medical Needs Want? A Qualitative Study of Patients' Views and Experiences with Expanded Access to Unapproved, Investigational Treatments in the Netherlands*. 20 BMC MED. ETHICS., 1, 80 (2019).

43 *Id.* at 37.

44 Moerdler S, Zhang L, Gerasimov E, *Physician Perspectives on Compassionate Use in Pediatric Oncology*, 66 PED. BLOOD CANCER, 6, 3 (2019).

45 Zettler ME, Jeune-Smith Y, Feinberg BA, Phillips EG, JD Pharm, and Gajra A. *Expanded Access and Right to Try Requests: The Community Oncologists' Experience*, JCO ONCOL. PRACT. (2021).

46 Chapman CR, Belli HM, Leach D, Shah LD, Bateman-House A. *A Survey of Pediatric Hematologists/Oncologists' Perspectives on Single Patient Expanded Access and Right to Try*, 5 MED ACCESS. 1–10 (2021).

47 *Id.* at 27, 32.

48 McKee AE, Markon AO, Kirk MC, Lurie P, *How Often are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved?* 57 CLIN. PHARM., 136–142 (2017).

49 Okie S, *Access Before Approval—A Right to Take Experimental Drugs?* 355 N. ENGL. J. MED., 5, 437–440 (2006).

who predominantly cared for patients with brain tumors and 1 radiation oncologist all of whom had experience with pursuing experimental drugs via either EAPs and/or RTT pathways.

II. METHODS

We undertook a qualitative approach as it permits a deeper understanding of the knowledge, ideas, beliefs, and motivations that shape the attitudes of clinical trialists since at the time of commencing the study, only one paper had been published on physicians' attitudes and experiences on RTT. Our literature review and preliminary research determined a strong rationale for picking cancer as a therapeutic area. The history of FDA challenges include access to unapproved cancer drugs (Laetrile, 1970s; Abigale Alliance, 2000s). And, FDA data show over a third of EAP requests are cancer related. Lastly, we could find no study examining RTT and EAP in the oncology context.⁵⁰

II.A. Recruitment

We used purposive sampling to identify neuro-oncologists who have experience with expanded access and/or RTT. Identification of experience with expanded access and/or RTT came from searches in [ClinicalTrials.gov](https://clinicaltrials.gov) along with networking with other neuro-oncologists in the field. Searches in [ClinicalTrials.gov](https://clinicaltrials.gov) identified studies and investigators listing participation in EAP. There were no restrictions on age, sex, or ethnicity, but all physicians had to currently be practicing in the United States.

We identified neuro-oncologists who participated as part of the multi-site GLIOGENE study as well as using [ClinicalTrials.gov](https://clinicaltrials.gov) to recruit neuro-oncologists with EAP and/or RTT experience. From the GLIOGENE study, 2 neuro-oncologists participated in our interviews. From [ClinicalTrials.gov](https://clinicaltrials.gov), we contacted 27 oncologists who participated in an Expanded Access Protocol for glioblastoma multiforme. After we contacted these 27 oncologists by email, 7 agreed to participate. We asked these initial participants to recommend additional possible participants, which resulted in recruitment of an additional 8 participants, for a total sample of 17 oncologists.

II.B. Interviews and Interview Guide

We developed a semi-structured interview guide based on findings from previous studies and modified it inductively after the first five interviews.^{51,52} The interview guide contains questions in 3 domains—knowledge, familiarity with EAP and RTT, and patient-physician conversations about unapproved drugs—totaling 14 questions (see Supplemental Information).

Informed consent was obtained verbally prior to beginning interviews. Interviews were conducted either by Zoom© or telephone and ranged from 43 to 63 minutes (averaging 53 minutes). Interviews were conducted by at least two members of the research team. Fourteen of these interviews were conducted by Haley Manley (HJM), eleven by Christopher Scott (CTS), six by Bryan Sisk (BS), and four by Zubin Master

50 Brower V. *Food and Drug Administration Responds to Pressure for Expanded Drug Access*, 106 J. NATL. CANCER INST. 6, 1–9 (2014).

51 *Id.* at 37, 43.

52 *Id.* at 41, 42.

(ZM). Interviews were audio recorded and professionally transcribed. This study was approved by Baylor College of Medicine's IRB (H-46177).

II.C. Codebook Development and Qualitative Analysis

Initial codebook development began with all members of the research team discussing two interviews identified as robust in terms of knowledge and experience with EAP and RTT. All team members added memos to transcripts individually, then collectively developed an initial codebook outlining possible themes. Two researchers (CTS and HJM) further analyzed additional transcripts to finalize the codebook which was then presented and discussed with all four team members. Qualitative analysis was performed using a modified grounded theory approach with constant comparison analysis.^{53,54} Transcripts were then individually coded and emergent themes were organized using Dedoose 8.3.47. A basic descriptive analysis was undertaken, followed by a comparison of codes within and between participants. Two rounds of abstractions were carried out to identify themes. Areas of confusion or disagreement were discussed and clarified through consensus. The full team reviewed and approved the final set of themes, definitions, and supporting quotes.

III. RESULTS

We interviewed 17 clinical researchers who had participated in oncology trials, represented by 15 different academic institutions from 10 different states with 8 females and 9 males. Sixteen oncologists focused on neurologic tumors, and one oncologist focused on neuroendocrine tumors. Nearly all participants were investigators on clinical trials for glioblastoma, and 4 participants were co-investigators on a multisite trial that mentioned EAP as a treatment option in their publications. Fifteen of 17 participants had previously completed at least one EAP protocol. Nearly half of our participants had patients who requested drugs through RTT, but only 3 had administered the experimental agent to patients through RTT.

Below, we describe 2 interrelated themes that influenced participants' views on EAP and RTT (summarized in [Table 1](#)).

III.A. Misconceptions and Confusion about EAP and RTT

Many physicians described having difficulty in distinguishing between RTT and EAP or demonstrated misconceptions in their responses. A physician with knowledge of both pathways spoke about his colleagues generally: 'I don't think a lot of people understand the difference between expanded access and Right-To-Try' [Participant 1]. The confusion resulted in conflation with the different features between EAP and RTT including structure, intent, and processes of these pathways. In response to our question 'Have you provided a drug through Right-to-Try?' one clinician erroneously replied, 'I think most compassionate use is under that category' [Participant 2]. Another drew a rough equivalence between the two despite the absence of FDA oversight for RTT: 'I guess the way I try to think about Right-to-Try is like compassionate use. If there's some

53 STRAUS A, CORBIN J. BASICS OF QUALITATIVE RESEARCH: GROUNDED THEORY PROCEDURES AND TECHNIQUE (1990).

54 CHARMAZ K. CONSTRUCTING GROUNDED THEORY (2014).

Table 1. Summary of themes generated from qualitative interviews of neuro-oncologists

Theme/subtheme	Explanation
Theme 1. Misconceptions and confusion about EAP and RTT	Physicians misconstrued definitions, processes, and provisions surrounding FDA's EAPs and the federal RTT law
Theme 2. Physicians' opinions, preferences, and experiences with EAP and RTT	
<i>Logistical barriers</i>	Physician experiences with EAP and RTT influenced their attitudes around administrative burdens and logistical barriers mostly surrounding IRB review and less so around FDA oversight
<i>EAP and RTT versus clinical trials</i>	Physicians largely preferred to involve patients seeking experimental medicine in clinical trials over non-trial pathways
<i>Case-by-case decisions</i>	Physicians describe those situations warranting preapproval access need to be determined on a case-by-cases basis taking into consideration the clinical circumstances of each patient
<i>Primacy of the patient's values</i>	Physicians respecting patient autonomy and expressing the need for patients to make the final decision on whether to pursue experimental medicine
<i>Physicians' motivations for pursuing EAP or RTT</i>	The differences of opinions among physicians for when it may be appropriate to use or not to use either expanded access or RTT pathways
<i>When physicians disagree with patients' desires or preferences</i>	Some physicians accept the use of unproven medicine for patients when it is not harmful to the patient or their treatment, but if the unproven medicine could cause harm, physicians would warn patients

sort of biologic or scientific rationale outside of any FDA authorization, and then if it is deemed safe by the physician, then you can prescribe that' [Participant 3]. Another physician defined RTT as 'where basically you can try repurposing drugs' [Participant 4]. This statement indicated that the physician confused off-label prescriptions with drugs available through RTT. A minority of physicians demonstrated a nuanced understanding about the differences between EAP and RTT. For example, one neuro-oncologist said '... if you read the law in more detail, it's not really right to try. It's more right to request. Right to try implies that the person would decide I want to try this and

I'm going to get it. Period. That's not actually what's written in the law. It really should be a right to request.' [Participant 6].

Physicians also described how some patients held misperceptions about EAP and RTT. For instance, one physician spoke of how patients have trouble understanding the development of clinical trials as it relates to EAP/RTT, I do spend a lot of time explaining the difference, phase one clinical trials are evaluating whether something's toxic to humans and phase two clinical trials, it's effective and not toxic. Then phase three, if it's effective against that particular tumor and that's how we get to standard of care. People don't seem to have any real understanding of this. They've even developed groups now who say, 'Nobody should have to settle for standard of care' [Participant 10].

One senior investigator attributed the rise of RTT to a general misperception by other patients, advocates, and physicians that the FDA was the primary barrier to access, "We've dealt a lot with Right-to-Try, and I think the people who are behind it don't really understand that the FDA is not really the barrier here" [Participant 1]. Another physician stated, "My understanding [is that our] patients could come to us and say, 'We have the right to try this drug.' But that still doesn't answer the question how we get the institutional support to give this drug and to do the oversight safety monitoring and things like that" [Participant 2].

III.B. Physicians' Opinions, Preferences, and Experiences with EAP and RTT

Our second major theme focused on physician's opinions, preferences, and experiences with off-trial pathways and were broken down into 6 subthemes: Logistical Barriers, EAP and RTT versus clinical trials, case-by-case decisions, primacy of the patient's values, physicians' motivations for pursuing EAP or RTT, and when physicians disagree with patients' desires or preferences.

Logistical Barriers

Physicians' past experiences with EAP and RTT seemed to influence their approaches and strategies for obtaining experimental medicines for patients. Though most physicians were neutral or positive about working with the FDA, some participants believed that overly rigid FDA regulations harmed some patients. This inflexibility drove one investigator to pursue RTT: '[The FDA] stated this might not be safe for the patient and I asked them has anyone complained? Taking this chance, I think it's very reasonable. In any kind of cancer therapy, you have this kind of toxicity. They [just] have to go by those guidelines and those rules that are given to them' [Participant 5]. Another participant perceived the changing requirements for submission of EAP requests were cumbersome, took precious time from clinical practice, and were costly: 'While I understand the good intentions of all these processes, it just seems like every year there's more and more added on . . . some of it is mandated at the federal level. And the thing I worry about more at the broader level is a lot of all of this really adds usually to the costs' [Participant 6].

When asked about specific barriers encountered in applying for EAP approval, participants mentioned deadlines and time delays imposed by local IRBs. For example, some physicians would forgo EAP if a local IRB was perceived to be a barrier to the efficient acquisition of a medication, regardless of how smoothly the interaction with the

FDA might go. When institutions had staff and infrastructure dedicated to supporting EAP, participants seemed to have more positive assessments of these pathways.

EAP and RTT Versus Clinical Trials

All participants suggested that they preferred other means of providing experimental drugs to patients including clinical trials and as off-label over EAP and RTT: “We basically always go clinical trial. If we can’t do clinical trial, then we’ll see if there’s anything out there that makes sense to use it as an EAP, and if not, one of the things that we do now for every single patient is molecular [targeting] A lot of institutions have their own home-cooked molecular analysis.” [Participant 1]. One reason for this preference was administrative: “For me, the biggest hurdle when it comes to expanded access is the amount of administrative work it actually takes . . . you have to write a five-page protocol and a consent form and then this will be reviewed by our pediatric scientific committee; then it will be reviewed by our cancer center, and then it has to get IRB approval in the midst of us getting FDA approval” [Participant 7]. Another reason was the desire to advance scientific knowledge, which clinical trials accomplished. Physicians also described how clinical trials provided reassurance about the biological plausibility of the treatment: “[A] lot of people have thought about this trial, and if they didn’t think it had any [biological plausibility], then most likely they will not offer it” [Participant 7]. In this way, the clinical trial provided the physician with more confidence in the decision to pursue unproven therapies. Others stated that they could not justify EAP or RTT when better alternatives exist: “If you’re talking to somebody who is at their very first recurrence of the disease and we’ve got other clinical trials available, and we’ve got other standard treatments available, then it’s like are we really going to go through the whole process of getting EAP for something which we really don’t know if it works when we’ve got other decent options on the table?” [Participant 8].

Case-by-Case Decisions

Many physicians expressed that decisions to pursue EAP or RTT needed to be made on a case-by-case basis, where clinical circumstances dictate the final decision. One oncologist said, “We look for an Achilles heel that could be an actionable mutation. If that actionable mutation has a drug that is commercially available, of course we’ll think of that. If it is an actionable mutation for which there’s investigational drugs, not commercially available, the only way to get it is an EAP, we would talk about it that way” [Participant 1]. However, another clinician said that a case-by-case basis is not how these decisions should be made: “My worry is that single use on a case-by-case basis, it doesn’t fulfill that general goal of learning from each patient case” [Participant 9]. Nonetheless, the participant later stated certain circumstances that might justify experimental treatments for specific cases: “I think we as oncologists . . . want to do what’s best for every single patient themselves, and there are sometimes very specific circumstances that might justify approaching otherwise investigational medical products in a way if they aren’t a trial candidate, that might still benefit a patient” [Participant 9].

Primacy of the Patient's Values

Although physicians themselves may have their own preferences for treatment, most expressed that the patient can decline an unproven drug, and physicians can decline to administer drugs if they are not in the patients' interest. However, physicians also described how patients might struggle to make logical decisions given their desperate conditions: "I would say despite those conversations, particularly in the world of brain tumor patients, that if you have a targeted drug and the tumor has the target 100 per cent of the time, despite that conversation, they're going to say, 'Give me the drug.' I've never had a situation where anybody turns it down, even when we talk about the risk-benefit" [Participant 10]. One physician described how he typically recommends palliative care when he feels experimental drugs or interventions could lead to morbidity, toxicity, and earlier death. However, he recounted one experience where he complied with a patient request for additional treatment, even though he did not believe the treatment would be effective. "We tried radiation and the patient died three days after completing the radiation. I understand how the emotion of that, of my relationship with those people, is what led me to make the wrong decision" [Participant 3].

Physician Motivations for Pursuing EAP or RTT

A few physicians expressed strong preferences for EAP rather than RTT even if they misunderstood the differences about them: "Right-to-Try is an abomination, it should never have been written. Nobody in the health care field wanted it written, not the FDA, not the [American Cancer Society], not anybody. It means that you're getting access to a drug from a company—not a physician—without the purview of the FDA. Makes no sense . . . We will never do right-to-try, and most physicians will not do right-to-try" [Participant 1]. However, most physicians did not make major distinctions between using either EAP or RTT. Instead, most described their approaches, in general, to accessing unproven medications for patients.

Clinicians described several motivations for pursuing EAP or RTT. Many discussed the importance of supporting the patient's hopes, particularly hope for survival: "I think hope is very important. Earlier on in my career I used to be very much of the mindset that you don't give false hope. You shouldn't try to give false hope. But over the years what I've seen is that for a lot of patients, hope is what keeps them going. They get very depressed when they don't have hope" [Participant 11]. Other times, participants described pressure to offer treatments and feelings of guilt if they did not offer treatments: "The husband said to me, 'Oh, so now we're just going to be left out in cold, huh? There's nothing else to do.' And that, it was just jarring emotionally to me, that I felt like I was abandoning these people that I really liked" [Participant 3]. Physicians also described a personal sense of urgency to do something—anything—for their patients: "In most cases it's desperation . . . You're just watching this tumor grow. People are desperate, and you want to help. You want to do anything you can to help." In neuro-oncology particularly, this desperation is exacerbated by a lack of proven treatment options: "This is neuro-oncology. We have exactly two treatments that have been approved by the FDA" [Participant 4].

Beyond these patient-focused motivations, some physicians described feeling a thrill from identifying a treatment for patients that others might have missed: "I mean, there's so much excitement to [finding a novel treatment] . . . I, selfishly, have some of that

excitement. I feel like I'm cracking a code or something, or that it's my ingenuity and drive that's going to bring those patients something, that's going to help them, that otherwise would not have happened.' [Participant 3]. Even when interventions failed to benefit the patients, physicians seldom found that patients were angry or upset about pursuing unproven agents: "This is a constant question we are asking ourselves, "Do they really understand?" I've never been surprised in the end, that then families were mad at us. It's always more we have a conversation like, "At least we tried." [Participant 7].

When Physicians Disagree with Patients Desires or Preferences

Despite these motivations to offer unproven medications, several physicians described situations where they disagreed with the patient's treatment preference. When this disagreement related to minor, non-harmful interventions, the physicians tended to accommodate the patient's preference: "If they want to take CBD oil because their friends, coworkers, aunt, took it and the breast cancer disappeared. I'll say, 'Great. There's no problem if you do that but I still think we should explore these other conventional therapies.' If the choice seemed harmful, however, several physicians described refusing the patient's request: "If I'm really not convinced it's a good idea, I definitely say no. If I really think this is not providing, or even doesn't have the potential to provide benefit . . . if I'm really not convinced, then I'm not offering this" [Participant 11]. This refusal could have implications on the patient's coping and hope: "You don't want to be Debbie Downer, unfortunately, that's sometimes how they will see you, as the one who is throwing sand in their face, and that you just aren't as hopeful as they seem to be in their fantasy. But you need to explain that there is a downside to all of this mad pursuit for the ephemeral cure" [Participant 12].

IV. DISCUSSION

Perhaps the most significant finding from our study showed that many oncologists were not fully aware of the differences between EAPs and RTT. The confusion around terminology among physicians and their understandings of the provisional differences between off-trial pathways has been well-documented. In one study conducted primarily at a single major medical center with three sites across the U.S., researchers observed confusion among clinical oncologists surrounding what the federal RTT law truly meant in terms of patients' right to accessing investigational drugs, the role of drug companies, IRB involvement, and the eligibility of drugs.⁵⁵ In one survey, confusion between EAP and RTT included conflation over structure, intent, and the procedural differences among the two pathways.⁵⁶ In this survey study of 238 physicians, only 27 per cent were able to identify the main differences between EAP and RTT.⁵⁷ In another study surveying pediatric oncologists, researchers found that acquiring drugs off-label was sometimes imprecisely considered EAP,⁵⁸ which was seen by one physician in our study. This disconnect was clearly apparent in our analysis of transcripts. Instances of conflation and confusion between EAP and RTT abound, with some

55 *Id.* at 37, 43, 51.

56 *Id.* at 45.

57 *Id.* at 45, 56.

58 *Id.* at 46.

investigators identified as participating in trials listing EAP as an option on [ClinicalTrials.gov](https://clinicaltrials.gov) having a limited understanding of that longstanding pathway of preapproval access. The lack of clarity around terminology among preapproval pathways and off-label prescribing is likely to contribute to confusion and possibly hinders patients' access to treatment.⁵⁹ Patients fortunate enough to have doctors familiar with the process and its associated terms are more likely to gain access to experimental treatments than those whose doctors are unaware of the options or not as adept at navigating preapproval pathways.⁶⁰

These results show a pressing need to better inform oncologists about preapproval pathways, including the differences among them and how best to navigate them. In a qualitative interview study where researchers informed oncologists about differences between EAP and RTT, several oncologists expressed a desire for greater education and resources to navigate preapproval pathways.⁶¹ There are several notable educational guides on the market including information produced by the American Society of Clinical Oncology and the Expanded Access Navigator developed by the Reagan-Udall Foundation for the FDA.^{62–65} Anecdotally, when we asked physicians about their awareness of some of these resources, many reported not knowing about them, which suggests that training programs for oncologists may be necessary in order to deliver information and resources about EAPs and RTT. Master et al., go a step further to posit that a natural extension of education would be to develop shared decision-making tools for oncologists in order to foster better patient-physician conversations about experimental cancer care in response to an individual patient's situation, desires, and available therapies.⁶⁶

A second major finding in our study was the level of administrative burdens associated with EAP, which are consistent with other studies, and includes concerns over the time and resources needed to secure the investigational product for patients and the timeliness of FDA and IRB reviews.^{67–69} Expanded access places some administrative

59 Beuttler KL, Shen MM, Caplan AL, Bateman-House A. *Pre-approval Access Terminology: A Cause for Confusion and a Danger to Patients*, 51 *THEOR. INNOV. REG. SCI*, 4, 494–500 (2017).

60 Darrow JJ, Avorn J, Kesselheim AS. *New FDA Breakthrough—Drug Category—Implications for Patients*. 370 *N. ENGL. J. MED.*, 1252–8 (2014).

61 *Id.* at 37, 43, 51, 55.

62 ASCO, *ASCO in Action Brief: Right-to-Try & Expanded Access to Investigational Drugs*, <https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/asco-action-brief-right-try-expanded-access> (accessed Aug. 3, 2021).

63 ASCO, *American Society of Clinical Oncology Position Statement on Access to Investigational Drugs*, <https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2017-Access-to-Investigational-Drugs-Position-Statement.pdf> (accessed Aug. 3, 2021).

64 ASCO, *Frequently Asked Questions Right-to-Try and Expanded Access to Investigational Therapies*, <https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/FAQs-Right-to-Try-Expanded-Access-to-Investigational-Therapies.pdf> (accessed Aug. 3, 2021).

65 *Id.* at 9.

66 Master Z, Adjei A.A., Hargraves I.G., Montori V.M., Tilburt J.C., *Responses to Martani, Tomasi, and Casanto*. 113 *JNCL*, 3, 340–341 (2021).

67 *Id.* at 37, 43, 51, 55, 61.

68 *Id.* at 46, 58.

69 *Id.* at 49.

burdens on physicians that RTT does not^{70,71}. To approve a request through EAP, both the FDA and IRB must authorize it. Once the physician has obtained approval from the drug company, they must then obtain local IRB approval prior to administering the drug, or else certify to the FDA that they meet conditions for a waiver of prospective IRB review.⁷² The IRB review can be a time-consuming process, especially since these submissions are often evaluated by people who might not be familiar with EAPs. One study evaluating IRB approval time at a Veteran Affairs Medical Center found that total review times ranged from 16 to 631 calendar days, with the median time for full board review being the longest (131 days).⁷³ This administrative delay affects physicians' decisions as to whether or not to use EAP as some in our study suggested they would forgo EAP if a local IRB was perceived to be a barrier to the efficient acquisition of experimental medication. In several cases our participants mentioned the IRB as a source of delay, with one respondent going so far to say his institution would not use EAP because of the local administrative burden. On the other hand, one interviewee praised her IRB in its knowledge of the fast-track features of EAP. Institutional-level deficiencies are supported by the literature: the authors in one study suggest IRBs are not a good fit for reviewing preapproval access requests; IRBs exhibit lack of uniformity of terms and policies, especially for single patient expanded access.⁷⁴ One rather simple step forward would be a preapproval access training module offered to research institutions through an organization such as Public Responsibility in Medicine and Research (PRIM&R). Recently, several efforts have been undertaken to promote the awareness of the EAP program and streamline the IRB process. For instance, a physician submitting the new form can request that a single IRB member (the chairperson or delegate) review the application, for the purpose of expediting the process.⁷⁵

While EAP application processes were once much longer and required more administrative steps, the FDA has reduced those thereby shortening timelines. The FDA has managed to streamline the process through Project Facilitate, to help oncologists request investigational cancer treatments for patients who are not eligible for a clinical trial or who have exhausted currently approved treatment options.⁷⁶ Prior to 2016, filing for a single patient EAP investigational new drug (IND) application required the same form as manufacturers had to complete for when filing an IND for a clinical trial.⁷⁷ In response to concerns of administrative burdens, the FDA developed a simplified two-page form (Form FDA 3926) which contains 11 instead of the 26 elements necessary for clinical trials.⁷⁸ Combining these attributes by the FDA along with other aspects

70 Fernandez LH, Sarpatwari A, Vonderheide RH, Zettler PJ. *Right to Try Requests and Oncologists' Gatekeeping Obligations*, 38 J. CLIN. ONC., 2, 111–114 (2020).

71 Lynch HF, Zettler PJ, Sarpatwari A. *Promoting Patient Interests in Implementing the Federal Right to Try Act*, JAMA, 320, 869–870 (2018).

72 Van Norman GA. *Expanding Patient Access to Investigational Drugs: Single Patient Investigational New Drug and the 'Right to Try'* 3 JACC BASIC TRANSL. SCI., 2, 280–293 (2018).

73 Hall DE, Hanusa BH, Stone RA, Ling BS, Arnold RM. *Time Required for Institutional Review Board Review at One Veterans Affairs Medical Center*. 150 JAMA SURG., 2103–109 (2015).

74 Folkers KM and Bateman-House A. *Improving Expanded Access in the United States: The Role of the Institutional Review Board*, 52, THER. INNOV. REGUL. SCI., 3, 285–293 (2018).

75 *Id.* at 45, 56, 57.

76 Walker, S. *Expanded Access Versus Right-to-Try*. 55 HOSP. PHARM., 2, 79–81 (2020).

77 *Id.* at 5.

to expedite the administrative processes outlined in Project Facilitate ie a telephone service, and requiring only review by a single member of the IRB, it is unlikely that the FDA itself is overly burdensome for most oncologists. Some of our participants somewhat acknowledged this sentiment indicating that FDA authorization procedures have improved. Given that oncologists in our cohort and from other studies really did not know about process differences between EAP and RTT, and that some preferred RTT when any administrative challenge was met, we wonder whether oncologists have a general aversion to any additional administrative work.

Since many oncologists in our study and evidence from other research show confusion about the administrative process of EAP, they may confuse where the challenges lie. Some oncologists in our study sought RTT as an alternative pathway to lower administrative burden and gain access to experimental medications to their patients faster. This suggests that education for oncologists needs to not only alert them to definitions and differences in the provisions between preapproval pathways, but to also provide insight into the value and reasons for why regulatory and ethics oversight is necessary. Expressing to oncologists the value of having FDA review ie knowledge into dosing and monitoring requirements, and IRB review of the ethics and informed consent aspects may suggest to busy physicians that these administrative hurdles are also necessary and serves to help them and their patients.

Proponents of RTT identify the FDA as the primary obstacle to accessing experimental therapies.⁷⁹ In one case in our study, a perceived lack of transparency at the FDA led to a wholesale adoption of RTT for a large cohort of terminally ill cancer patients. In this case, the investigator was trying to procure a drug that was approved in the EU but not yet by the FDA, and used his state-level RTT to source the drug. Eventually, the drug in question was approved by the FDA, but long after the critical period of access had passed for his patients. For all EAP categories, the FDA must determine that the condition is serious or immediately life-threatening, that there are no similar or satisfactory alternative therapies, and that access will not interfere with pivotal clinical trials.⁸⁰ Additionally, the FDA must determine the potential benefits outweigh the risks.⁸¹ Nonetheless, although RTT supporters suggest that FDA decision making and timing interferes with obtaining investigational drugs, studies such as those conducted by Zettler et al. demonstrate that RTT is no more successful than EAP in gaining access to unapproved drugs.⁸² What seems to be a significant barrier to obtaining experimental therapies is the manufacturer rather than the FDA.

Seven oncologists in our study reported that the major obstacle in accessing experimental therapeutics was receiving approval from drug manufacturers. Major points included in the difficulties in working with small biotechnology companies, time

78 The Food and Drug Administration, *Individual Patient Expanded Access Investigational New Drug Application (IND)*, <https://www.fda.gov/media/98616/download> (accessed Sept. 7, 2021).

79 Holbein ME, Weatherwax KJ, Gravelin M, Hutchinson R, and Mashour GA, *Right now, in the Right Way: U.S. Food and Drug Administration's Expanded Access Program and Patient's Rights* 2 J. CLIN. TRANS. SCI., 115–117 (2018).

80 The Food and Drug Administration, *Title 21*, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.305> (accessed Aug. 4, 2021).

81 Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*. 372 N. ENGL. J. MED., 3:279–86 (2015).

82 *Id.* at. 45, 56, 57, 75.

constraints in obtaining drugs for terminally ill patients, and the fact that provision of drugs is discretionary. On this last point, manufacturers face a number of challenges; they may worry that providing access outside of trials could deplete their limited supplies of experimental products, make them liable for injuries to patients, and make eventual FDA authorization less likely either because of adverse events that develop or by deterring patients from enrolling in ongoing clinical trials.⁸³ Even if the manufacturer is willing to provide an experimental drug for expanded access, the drug might be too expensive and difficult to produce to allow for administration without participation in a clinical trial.⁸⁴

Further approaches for lessening the administrative burden between physicians, the IRB, and the FDA have been suggested such as states partnering with the FDA to fund multicenter IRBs that focus specifically on EAP requests.⁸⁵ Others have that an independent board of clinicians could determine whether a patient satisfies the criteria for EAP to streamline the review process.⁸⁶ One study evaluating oncologists' experiences with RTT cited administrative personnel with expertise in these programs as a crucial resource for reducing burdens and easing the clinical responsibility of physicians.⁸⁷ Along with improved institutional knowledge, these solutions seem reasonable, especially for the types of oncologists we interviewed for our study.

Although RTT requires approval from drug manufacturers as well, the other administrative hurdles of EAP formed the basis for why a few of our oncologists used RTT. Albeit many of our oncologists suggested they did not pursue RTT because of its procedural and legal ambiguity, some used it for its simplicity. Federal and state based RTT laws generally lack provisions of FDA and ethics review and permit faster access but at the possible costs to patients.^{88–90} While a vast majority (78.3 per cent) of 83 IRB members surveyed among different institutions indicated that it was important for a designated member of the IRB to review single patient EAP requests, 16.8 per cent disagreed or strongly disagreed with such a statement.⁹¹ Interestingly, most respondents supported a single designated reviewer policy but 65.1 per cent of participants reported that full board review was necessary.⁹² These findings would suggest that the need for further insight into the value of IRB review is required in order to assess its importance and further streamline the process (if necessary). In addition, while respondents in

83 *Id.* at 18, 20, 23, 30.

84 Laney J, *The Shifting Landscape of Medicine: Patents of Personalized Biologic Treatments and Their Potential Conflicts with Right-to-Try Laws*, 26 J. INTEL. PROP. LAW, 1, 159–172 (2019).

85 *Id.* at 81.

86 Jerome RN, Edwards TL, Boswell HC, Bernard GR, Harris PA, Pulley JM. *Recommendations to Facilitate Expanded Access to Investigational Therapies for Seriously Ill Patients*. 3 ACAD. MED., 305–9 (2016).

87 *Id.* at 36, 43, 50, 54, 60, 66.

88 Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. *I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy*. 86 CLIN. PHARMACOL. THER., 97–100 (2009).

89 Agarwal R, Saltz LBH, *Understanding the Right to Try Act*, 26 CLIN. CANCER RES., 2, 340–343 (2015).

90 Spector-Bagday K, Weatherwax KJ, Gravelin M, Shuman AG, *The Critical Role of Medical Institutions in Expanding Access to Investigational Interventions*, 49 HASTINGS CENT. REP., 2, 36–39 (2019).

91 Chapman CR, Shearston JA, Folkers KM, Redman BK, Caplan A, and Bateman-House A, *Single-Patient Expanded Access Requests: IRB Professionals' Experiences and Perspectives*, 10 AJOB EMPIR. BIOETH., 2, 88–99 (2019).

92 *Id.* at 89.

the study were quite familiar and responsive to EAP requests, other IRBs may be less familiar with the EAPs.^{93,94}

Although the FDA authorizes over 99 per cent of EAP requests and has created Project Facilitate to further streamline processes, it remains unclear how many oncologists are deterred from fully completing the necessary administrative procedures of filing an EAP IND or submitting IRB review because of actual or perceived administrative barriers. Several studies of provider attitudes suggest streamlining EAP processes as opposed to abandoning them and thus further research is needed to better understand administrative pain-points.^{95,96} Organizations such as academic health centers have the infrastructure, intellectual capital, and high-quality care and research to accommodate units or groups within it to help facilitate EAP requests.^{97,98} It would be plausible to add such groups within hospitals or medical centers that could facilitate procedural steps for physicians, but this would be a resource intensive effort and unlikely to be adopted by smaller institutions.

There are several limitations to our study worth noting. First is our small sample size of 17 oncologists. Despite this small sample we did see saturation and our data mirrors results in other published works.⁹⁹ Additionally, physicians' responses in our study are self-reported and thus subject to recall bias. Furthermore, our focus on brain cancers might not reflect the experiences of all other oncologists, or the perspectives of non-oncology physicians and researchers. Also, all participants in this study were from academic centers and were familiar with clinical trials. As such, these results might not represent the experiences of oncologists at non-academic centers.

V. CONCLUSIONS

This study represents an initial investigation evaluating misconceptions, barriers, and experiences with EAP and RTT. Despite experience with obtaining experimental cancer drugs for their terminal patients, clinicians continue to express confusion over the two pathways even three years after the passing of federal RTT legislation. Clinicians considering RTT or EAP must balance patient and family hope, and importantly, perceived, or real views about institutional, government or corporate impediments to obtaining interventions when time for the patient is short. Additional work is needed to understand how best to support physicians as they consider investigational therapies for their patients. The results of our study also demonstrate that physicians need to be better informed about the differences in off-trial pathways, especially the differences between these pathways, clinical trials, and off-label medicine. These findings illustrate the importance of clinicians' experiences with experimental medicine and how preliminary experiences impact their future clinical care as well as opinions and motivation to implement these therapies going forward.

93 *Id.* at 78.

94 *Id.* at 87, 88.

95 *Id.* at 37, 43, 51, 55, 61, 67, 87.

96 *Id.* at 84.

97 *Id.* at 86.

98 Bernard GR. *Preparedness of the CTSA's Structural and Scientific Assets to Support the Mission of the National Center for Advancing Translational Sciences (NCATS)*. 5 *CLIN. TRANSL. SCI.*, 121–129 (2012).

99 *Id.* at 37, 43, 51, 55, 61, 67, 87, 95.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr Melissa Bondy at Stanford University for her ongoing support of this project. This research was supported by NIH/NCI 3R01CA217105-02S1 and the National Center for Advancing Translational Sciences (UL1 TR002377), NIH HHS/United States.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.