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Before Consent: Qualitative Analysis of Deliberations of Patients With Advanced Cancer About Early-Phase Clinical Trials

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QUESTION ASKED: How do patients with advanced cancer deliberate about joining an early-phase clinical trial before the consent process, and how do these deliberations facilitate or impede trial enrollment?

SUMMARY ANSWER: Early-phase trial deliberations occurred during two phases, which we labeled setting the stage and securing a seat. Setting the stage occurred when patients expressed an interest in a trial, and oncologists supported their pursuit of trial initiation. Securing a seat was the process by which oncologists and patients identified whether there was a study available that the patient could join as well as whether the patient met the eligibility criteria of the study.

WHAT WE DID: We conducted a comparative ethnography of early-phase trial enrollment at two academic medical centers in different regions of the country. We recruited 92 patients with advanced cancer who were believed by their oncologists to be on the cusp of exhausting standard treatment options and observed them for an average of approximately 7 months. We gathered data by observing one to four clinic visits and conducting one to four in-depth interviews with each patient as well as interviews with oncologists and patient-identified caregivers. Using computer software, multiple analysts thematically coded the data and used constant comparative methods to inductively develop a two-phase model of early-phase trial enrollment. We then used framework analysis to examine the utility of the model for describing the experiences of the entire study cohort.

WHAT WE FOUND: Progress toward early-phase enrollment was neither linear nor the default. Rather, it required reaching four milestones (patient interest, provider support, trial availability, and patient eligibility), each with different timelines, criteria, and actors. Enrollment was therefore like solving a Rubik's cube (ie, it involved working on and solving multiple interconnected puzzles simultaneously rather than following the steps of a predetermined pipeline or pathway from standard of care to experimental study).

BIAS, CONFOUNDING FACTORS: This study sought to capture the rich context of trial deliberations rather than produce generalizable results. We used a number of strategies to mitigate selection bias, but the study included only English-speaking patients, and we relied on treating oncologists to support recruitment.

REAL-LIFE IMPLICATIONS: Solving the Rubik's cube of early-phase enrollment more quickly and reliably may require well-coordinated and thoughtfully timed intervention strategies that start well before the consent process. With no readily apparent single bottleneck to enrollment, it may also be important to further examine strategies to identify structural factors that take current enrollment processes out of patients' and clinicians' control.

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abstract

PURPOSE Patients with advanced cancer and oncologists deliberate about early-phase (EP) trials as they consider whether to pursue EP trial enrollment. We have limited information about those deliberations and how they may facilitate or impede trial initiation. This study describes these deliberations and their relationship to trial initiation.

PATIENTS AND METHODS We collected longitudinal, ethnographic data on deliberations of patients with advanced cancer at two academic medical centers. We used constant comparative and framework analyses to characterize the deliberative process and its relationship to trial initiation.

RESULTS Of 96 patients with advanced cancer, 26% initiated EP enrollment and 19% joined a trial. Constant comparative analysis revealed two foci of deliberation. Setting the stage focused on patient and physician support for EP trial involvement, including patients' interest in research and oncologists' awareness of trials and assessment of patient fit. Securing a seat focused on eligibility for and entrance to a specific trial and involved trial availability, treatment history, disease progression, and enrollment timing. Patients enrolled in a trial only when both stages could be successfully navigated.

CONCLUSION Ethnographic data revealed two foci of deliberation about EP trial enrollment among patients with advanced cancer. Physician support played a consequential role in both stages, but enrollment also reflected factors beyond the control of any specific individual. Insights from this study, combined with other recent studies of trial enrollment, advance our understanding of the complex process of EP trial accrual and may help identify strategies to improve rates of participation.

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INTRODUCTION

Patients with advanced cancer may be offered the opportunity to join an early-phase (EP) clinical trial (eg, a single-arm study to examine dosing and safety of therapies previously untested in humans).[1] EP trials provide a lens for understanding research participation in circumstances when patients are terminally ill and lack therapeutic options.[2,3] To date, this lens has focused largely on consent and enrollment. Researchers have examined which patients tend to enroll in EP studies (higher income and education) and whether participants understand the purposes (many do not) and therapeutic benefits (many overestimate benefits) of these trials.[4-11] Studies have shown that patients who review an informed consent document typically enroll,[11-13] and many potentially eligible patients never have the opportunity to consent.[14-16] Although these patterns have been repeatedly documented, we have only limited insight into their implications.[15,17,18]

This study sought to provide a rich understanding of how patients with advanced cancer, oncologists, and caregivers discuss and deliberate about EP trial participation in everyday life. By analyzing these deliberations longitudinally, from the perspective of multiple stakeholders and among patients who both enrolled and did not enroll in an EP trial, we sought to provide a fuller understanding of factors that may facilitate or impede EP trial participation. This rich understanding of the EP process is relevant for the continuing advancement of cancer discovery and complements similar efforts to document the dynamics of trial participation.[19]

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PATIENTS AND METHODS

All procedures were institutional review board approved, and all participants provided informed consent. We use pseudonyms to protect confidentiality.

Design

We used an ethnographic design, an observational technique to investigate culture and social interactions.[20] We collected data via direct observation of clinic interactions; in-depth one-on-one interviews with patients, caregivers, and clinicians; and a survey of patients and caregivers. Sites included eight multidisciplinary clinics at two National Cancer Institute–designated Comprehensive Cancer Centers with active EP programs. The primary site was the Pacific Cancer Center (breast, genitourinary [GU], GI, and melanoma clinics); we conducted comparative ethnography at the Midwest Cancer Center (GU, GI, gynecologic, and lung clinics).

Recruitment and Data Collection

Patients with advanced cancer whom clinicians judged would soon exhaust standard therapies and who could communicate effectively in English were eligible to participate in this study. We identified all patients with stage IV cancer who had upcoming appointments in study clinics, and a trained fieldworker then attended the clinic to confirm potential eligibility with a patient's treating oncologist. Fieldworkers also asked treating oncologists to introduce the fieldworker and study to the patient. We provide additional details of our recruitment procedures and the multiple strategies we used to avoid selection bias elsewhere.[14,21] With patient and caregiver consent, the fieldworker observed the visit and invited the patient to participate in the study.

To collect data, we observed up to four clinic visits and conducted 45- to 90-minute in-depth, semistructured interviews with patients (one to four interviews), caregivers (one interview), and clinicians (one interview). Patient and caregiver interviews addressed: clinic visits, health history, decision making, knowledge of clinical trials, social support, and spirituality. Clinician interviews addressed patient care responsibilities, professional background, trial recruitment activities, and view of EP trials.

Data Management and Analysis

Interview recordings were professionally transcribed, longhand observational field notes were word-processed, and all data were placed in ATLAS.ti software.[22] We drew on scholarly literature and fieldwork experiences to develop a codebook of themes. We coded all data and double coded 20% of the data to ensure rigor. Finally, we constructed analytic case summaries to capture key themes, events, and outcomes for all patients.

Our study outcomes were trial enrollment (signed consent) and trial initiation, which we have shown elsewhere is a significant step toward trial enrollment.[14] Initiation occurred when a patient was referred to the phase I clinic at either the Pacific or Midwest site or when a patient reviewed an EP consent form at the Midwest site. Working with a subsample of 22 Pacific patients (trial initiates, n = 11; noninitiates, n = 11), we used constant comparative analysis to inductively construct a model of how EP deliberations affected trial initiation and enrollment.[23] We validated this model with the full data set using the framework method.[24,25] The case summaries and framework method allowed us to characterize the relatively frequency of particular events in our coded data set. Our results drew on these analyses to report the substantive importance of certain outcomes, using terms such as most, majority, and few.

RESULTS

Of 96 patients (Pacific, n = 78; Midwest, n = 18), 25 initiated an EP trial and 18 enrolled. Pacific patients were more likely to initiate an EP trial (27% *v* 22%). Most patients were seen in GI or GU clinics, two of five were women, and two thirds were white. Our sample was well educated; three fifths had a college degree. We observed patients an average of 224 days at Pacific and 94 days at Midwest, averaging two observations and two interviews (Table 1).

TABLE 1. Characteristics of Patient Deliberation Study Sample (N = 96)

Characteristic	No.	%
Field site		
Pacific	78	81
Midwest	18	19
Disease site		
Breast	17	18
GI	32	33
Genitourinary	30	31
Gynecologic	2	2
Lung	2	2
Melanoma	13	14
Female gender	39	41
Race/ethnicity		
African American	9	9
Asian/Asian American	11	11
White	61	64
Other or multiracial	6	6
Hispanic	4	4
Less than a bachelor's degree	35	36
Age < 65 years*	56	58
EP trial initiation	25	26
EP trial enrollment	18	19

Abbreviation: EP, early phase.
*Mean age, 60.5 years.

Patient deliberation during the period before consent included two processes, which we labeled setting the stage and securing a seat. When setting the stage, patients and clinicians explored the possibility of research participation and confirmed that a patient wanted to consider an EP study. When securing a seat, clinicians and patients identified an open trial, affirmed patient eligibility, and obtained informed consent. Patients who enrolled in an EP trial had to satisfy both steps. Setting the stage typically, but not always, occurred before securing a seat. All patients' deliberations involved setting the stage; fewer advanced to securing a seat.

Process One: Setting the Stage

To set the stage, patients had to express interest in EP trial involvement, and physicians had to support their patients' involvement.

Patient interest. Most patients in the cohort knew about clinical trials, but fewer than half were familiar with EP trials specifically. Some patients experienced rapid disease progression and died before becoming aware of EP studies; some experienced disease stabilization, so an EP trial never arose as a possibility. Among those aware of EP trials, some worried about adverse effects or about being in an experiment that might not slow disease progression. "I didn't want to try something that wasn't more of a definite" (interview, female patient; age group, 50 to 59 years; rectal cancer; Midwest site). However, nearly all who were aware of EP trials were open to them as a potential option.

Not surprisingly, many patients became interested in an EP trial when their oncologist recommended they consider it. But others' interest arose outside the clinician-patient relationship. A Pacific patient, for example, did online research to find and advocate for an EP trial at a different cancer center, because the Pacific-based trial she wanted to join was not yet open (female patient; age group, 50 to 59 years; breast cancer). Several patients had friends or family members in biomedical professions who encouraged and researched clinical trial involvement. Even when such guidance did not focus on EP trials, it fostered an interest in clinical research that extended to EP studies.

Some patients were interested in EP trials because they hoped it would be clinically efficacious—the opposite of patients who avoided trials because they worried it would not help them personally. "I still believe there can be a miracle," a Midwest patient said about an EP trial. "I'm hoping it will help my cancer" (female patient; age group, 50 to 59 years; endometrial cancer). Hope for personal benefit was not inconsistent with a desire to contribute to science. "I'm an optimist," one Pacific patient explained, "so I'm hoping that the trials turn out better than the already approved procedures. And other people will benefit from what I do" (male patient; age group, 70 to 79 years; prostate cancer). Other patients believed EP trials were their only remaining medical option, leading to situations in which patient interest in a specific EP trial seemed to intensify when there were few available study seats.

Finally, in our sample, interest in an EP trial did not necessarily reflect accurate knowledge. More than a few patients expressed an interest in EP trial participation even though they could not accurately describe the trial they hoped to join or the purpose of phase I trials in general. A retired scientist who described himself as interested in trials, for example, knew he was in an "early" phase trial but could not identify the phase or explain what it meant (male patient; age group, 70 to 79 years; GU cancer; Pacific site).

Physician support. Many oncologists supported EP trials among patients who had few remaining standard treatment options, although some did not discuss EP trials with patients who were responding to standard treatment. In practice, many oncologists expressed support for EP studies even as they continued to discuss or recommend standard therapies, thus interweaving the prospect of an EP trial with conversations about approved treatments. For example, a breast oncologist at Pacific, even as she recommended standard chemotherapy, included an EP trial among the several possible studies a patient might consider if her disease progressed. A GI oncologist at Pacific explained to a patient with stomach cancer that there were a variety of standard chemotherapies, but "if there's a good [EP] trial it might be good to try one of those first" (field note [FN]; male patient; age group, 40 to 49 years; GI cancer; Pacific site).

In describing EP trials, some oncologists highlighted their uncertainty. For example, one Midwest oncologist noted, "There's no way to predict which will work…. Phase Is are always a long shot" (FN; female patient; age group, 50 to 59 years; endometrial cancer). However, more often, oncologists supported such trials. Some communicated general enthusiasm by noting that studies were "exciting" or "interesting." Some oncologists expressed even stronger support, such as the Pacific oncologist who told a patient with a rare genitourinary cancer (male patient; age group, 70 to 79 years), "Part of the reason that [hospital] sent you up here was to try things like this…. I think there's a shot that it might work for your cancer…. The study is about to close, and I think you would be a good candidate…. There are risks, but there may be some promises, too. If it doesn't work, we can always go back to mitotane" (FN).

Patients relied on their providers to refer them to an EP trial or clinic. These referrals thus were arguably the most consequential form of support an oncologist could provide. Oncologists' perception of a study drug could shape their enthusiasm for taking this step. Oncologists tended to be more supportive of a patient's consideration of an EP trial when, in their clinical judgment, the study drug seemed potentially effective. Oncologists also often assessed the patient's potential to succeed in the EP trial holistically, beyond just his or her clinical eligibility. In some cases, this

holistic assessment increased oncologists' support for EP trial initiation. One Pacific provider cited a patient's geographic proximity to clinic, strong social support, and physical well-being as reasons he or she would be a good fit for an EP trial. In other instances, oncologists did not support EP trial initiation because of holistic factors such as patient struggles with substance abuse, concern about a patient's comprehension of study procedures, or perception that the patient would be unable or unwilling to adhere to study protocols.

Process Two: Securing a Seat

To secure a seat, clinicians had to match an eligible patient with an open trial.

Available trial. Pacific and Midwest opened many EP trials, but each trial was small, and therefore, experimental seats at each institution were scarce. Oncologists kept abreast of the trials each institution at weekly meetings, and at these meetings, clinicians typically discussed whether a particular trial might be appropriate for a particular patient. These discussions could motivate a clinician to explore that patient's interest in joining a study, and when clinicians knew a trial was in high demand or had few remaining seats, they sometimes encouraged decisive action. In one instance, for example, a Pacific patient reviewed a trial, consulted with phase I clinicians, and consented to the study within 2 weeks of learning of disease progression to join the trial before it closed to accrual (male patient; age group, 70 to 79 years; Leydig cell tumor).

In some cases, interested patients and providers struggled to find an available trial seat. A Pacific patient with esophageal cancer took home a consent form, but the trial closed before he decided whether to enroll (male patient; age group, 70 to 79 years). A Pacific patient with breast cancer had tried to participate in an EP trial at a different institution, but an unexpected drug shortage prevented her enrollment (female patient; age group, 50 to 59 years). She pursued EP trial involvement at Pacific and ultimately enrolled in a trial at the other institution when the drug shortage was resolved.

Eligible patient. At both Pacific and Midwest, EP trials included complex clinical eligibility criteria, and clinicians typically did not begin the process of formally assessing a patient's eligibility until the patient had initiated trial enrollment and a potential seat had been identified. At this point, clinicians might determine that a potential patient could not participate because of comorbidities or previous treatment. Some trials required a washout period before enrollment.

Several patients in our cohort set the stage to join an EP trial and even identified an available seat only to not meet trial eligibility criteria because of brain metastasis, previous cancer diagnosis, or prior treatment, among other reasons. A few patients formally enrolled in a study but never received the experimental treatment because of sequelae of disease progression (eg, persistently low platelets [male patient; age group, 70 to 79 years; esophageal cancer; Pacific site] or functional status deterioration [male patient; age group, 60 to 69 years; lung cancer; Midwest site]).

Clinicians' understanding of eligibility criteria also shaped patients' EP trajectory early in the process. While setting the stage, clinicians informally assessed whether a patient might be eligible for an EP study. One oncologist explained that he believed his patient was ineligible for an EP study because he had two types of cancer and so had no plans to refer him to the EP clinic (age group, 60 to 69 years; lung cancer; Pacific site). Another clinician felt her patient with liver cancer was "too sick" to participate in an EP trial, so she never presented this option (male patient; age group, 70 to 79 years; Pacific site). A Pacific patient who sought to aggressively treat his metastatic esophageal cancer was willing to "fly to the ends of the earth" to enroll in a clinical trial (age group, 50 to 59 years; esophageal cancer). His oncologist agreed the patient might benefit from study participation, but he learned before referring the patient to the EP clinic that the patient did not meet eligibility criteria for any available study.

Enrollment and nonenrollment

As listed in Table 2, 18 patients (19% of the cohort) enrolled in an EP trial, and 78 patients (81%) did not. We were able to identify when the enrollment process failed for 64 patients (85% of those who did not enroll): trial unavailability (24%), lack of provider support (21%), patient ineligibility (13%), and lack of patient interest (9%). Table 3 lists additional details of the EP trial enrollment process.

DISCUSSION

Among 96 patients with late-stage cancer observed for an average of 7 months at two cancer centers, 26% initiated an EP trial and 19% ultimately enrolled. Multiple studies have shown that enrolling patients with cancer in clinical research is challenging, because few patients enroll among

TABLE 2. Barriers to Patient Participation in EP Oncology Trial (N = 96)

Barrier	No.	%
Primary barrier identified		
Setting the stage		
Patient interest	9	9
Provider support	20	21
Securing a seat		
EP trial availability	23	24
Patient eligibility	12	13
Could not identify barrier	14	15
No barrier; patient enrolled in trial	18	19
Total	96	100

Abbreviation: EP, early phase.

TABLE 3. Deliberations and Achievements Preceding EP Trial Enrollment

Stage	Criteria to Achieve	Actors Involved	Timing
Setting the stage			
Patient interest	Patient becomes open to participating in EP trial; many patients are enthusiastic and proactive	Patient, provider, patient's social network	Varies substantially by patient; some express interest at debut of care, others in response to provider or network suggestions or as disease progresses; interest and openness vary over time
Provider support	Provider views patient as good trial candidate (eg, potentially eligible for and able to fulfill typical EP trial requirements, few remaining standard treatment options)	Provider, patient, communication from EP trialists	Providers evaluate patients' candidacy for and openness to EP trials over course of their care; referral to EP trial may occur before or after patient exhausts standard therapies
Securing a seat			
Available trial	Trial relevant and accessible to patient is actively recruiting; may be identified by provider, patient/patient network, or EP clinic	EP trialists, provider, patient, patient network	Relevant EP trials come and go as patient receives care; trial seat must be available at same time that all other criteria are met
Eligible patient	Patient's medical history, current and past cancer treatments, disease characteristics, and disease progression are consonant with provider's understanding of EP eligibility factors (earlier) or all conform to eligibility of specific trial (later)	Patient, provider, EP trialists	Earlier: eligibility criteria of current/recent EP trials shape oncologists' considerations regarding whether and how to engage patients in EP discussions Later: criteria filter out patients at time of formal trial recruitment and enrollment

Abbreviation: EP, early phase.

those who seem eligible. Granular qualitative data from this study document the nature of the enrollment challenge. Patients enrolled in an EP trial only when patient interest and oncologist support set the stage and patients met the strict eligibility criteria of an available trial to secure a seat. Our data highlight the complexity and interrelatedness of these processes. Progress toward EP enrollment was neither linear nor the default. Rather, it required reaching four milestones (patient interest, provider support, trial availability, and study eligibility) that each involved different timelines, criteria, and actors. Achieving EP trial enrollment resembled solving a Rubik's cube: the simultaneous and coordinated solution of multiple interconnected puzzles.

In previous studies of EP enrollment, ethicists examined consenting discussions, with a focus on patient understanding, expectations for experimental treatment, and dilemmas associated with therapeutic misconceptions.[8,26-28] Such studies reported high rates of enrollment among those who viewed a consent form,[29] but this may provide limited insight into other factors that shape enrollment.[30] As we show here, by the time patients initiated the EP trial process, most had nearly solved the Rubik's cube of enrollment. Outcome researchers have used pipeline models to examine enrollment,[6,30,31] barriers to enrollment,[32-34] and oncologists' role in enrollment.[17] These models have focused on factors that may cause patients to "leak out" of the trials pipeline (eg, disease progression or eligibility criteria).[35] A big-data analysis by Unger et al[36] suggest that such models, although intuitively appealing, may not capture the complex reality of trial recruitment and may overstate patient decision making and underemphasize oncologists' role. This ethnographic study, similarly, suggests the need to explore the utility of nonlinear models of trial enrollment.

We found that initiation and enrollment emerged during an extended period of deliberation that featured communication and interaction among patients and providers—interactions shaped by institutional, scientific, and clinical factors beyond the control of either party. Our results affirm that oncologists play a central role in EP trial initiation, but their role is more nuanced than that of facilitator or gatekeeper. Their ability to set the stage and secure a seat was constrained by the difficulty of knowing whether a seat was available. The counsel they offer patients during the deliberative process reflected their clinical judgment, including their knowledge that few patients successfully enroll in an EP study and even fewer benefit. Our data suggest that oncologists' hesitance to support patients' enrollment and the lack of available trials impeded EP participation more often than a failure of patient interest—insights that differ from those of studies focused exclusively on the later stages of this process[29,37] or on cancer clinical trials more broadly.[38]

Appreciating the dynamics and context of EP trial deliberation may help identify targets for interventions to improve the process. Currently, efforts to improve trial enrollment focus on improving patient understanding of trials, addressing logistic challenges, and broadening inclusion criteria.[19,39-41] In our study, even highly motivated and

resourceful patients found enrollment challenging, so improving patient knowledge may be part of an effective intervention but may not be a panacea. Our results also suggest that the timing of interventions matters. For example, navigators may be most helpful addressing logistic challenges while clinicians set the stage, and broader inclusion may help patients secure a seat. Structural changes may also be valuable, such as allowing patients to visit EP clinics long before standard treatment options are exhausted. Mostly, our findings suggest the value of instituting multiple changes simultaneously, because enrollment challenges arose throughout the process, not at a single bottleneck.[1,13]

Our study does have limitations. Ethnographic studies are not typically generalizable, and we designed this study to capture the rich context of trial deliberation at two study sites rather than to produce widely generalizable results. Years of ethnography in multiple clinics have revealed some differences (eg, in length of follow-up) but mostly suggest that EP trial deliberation and enrollment at our two geographically distant study sites were similar. Thus, our results may have relevance for other academic medical centers. We used techniques to mitigate selection bias, but our study included only English speakers, and we relied on treating oncologists to affirm patients' eligibility and introduce us to patients. These limitations could have produced a biased sample. Importantly, future work should examine how well the processes we describe apply in settings where patients are more diverse in terms of race, ethnicity, education, and income.

In conclusion, this study documented how patients with advanced cancer navigate EP trial participation as therapeutic options dwindle. We found that trial enrollment emerged (or not) in conversation and interaction between clinicians and patients over time, but crucial aspects of this process were out of patients' and clinicians' control. We also found no well-established pipeline to recruit patients into EP trials. Rather, enrollment occurred when multiple interconnected factors aligned simultaneously. Enrollment was akin to solving a Rubik's cube, not traversing a pipeline. As ethicists and policymakers consider ways to improve EP participation, this Rubik's cube model may prove a useful way to approach improving this period of the cancer journey.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Before Consent: Qualitative Analysis of Deliberations of Patients With Advanced Cancer About Early-Phase Clinical Trials

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