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From the other side: The patient perspective on cancer clinical trials

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Abstract

This article provides the patient perspective on cancer clinical trials.

(1) How do patients find them?
(2) What design elements are important to patients?
(3) What are some of the criteria patients use to determine whether to participate?
(4) What expectations do patients have of clinical staff?
(5) What should be done to disseminate results?

Keywords: Cancer; Clinical trial; Patient; Perspective; Shared decision-making; Search; Clinicaltrials.gov; Placebo; Side effects; Logistical burden; Financial burden; Financial toxicity; Treatment; Experiment; Researcher; Clinician; Dissemination; Participant; Design; Standard of care; Physician; Cancer.gov; Second opinion; Tumor; Equipoise

Introduction

Cancer clinical trials in the United States have low awareness and are largely misunderstood by patients, resulting in adult participation levels estimated at roughly 3% [1]. This article provides the patient perspective on cancer clinical trials and explain the challenges and opportunities of delivering new standards of care in an age of accelerated discovery and increasing patient-centricity.

Tapping the pipeline: Finding cancer clinical trials

With low awareness and limited access, the search for a clinical trial never starts for many patients. They do not know to ask and their diagnosing physician may not have one to suggest. Beyond that, the subject of a trial may not even be discussed despite an estimated 86% of Americans believing that trials should be discussed as standard of care and 74% indicating a willingness to participate if asked by someone that they trust [2]. Though patients expect their oncologist to inform them about clinical trials [3], only 41 percentage of cancer survivors in a Cancer Support Community survey recalled having a discussion about clinical trials with their health care team [4].

Social media and institutional review board approved (as per FDA guidelines [5]) advertising are changing this dynamic, building awareness and connecting people to trials. But the primary lead for trials has been and will continue to be the diagnosing clinician or a referral.

As patients typically do not search for trials on their own, clarity can come from clinical trial navigation services. Patients who choose self-service using online search tools will need technical details about their diagnosis and are typically overwhelmed by the complexity of applying them to search parameters and filters. As of July 2017, the de facto global clinical trial registry—www.clinicaltrials.gov—listed over 3,600 prostate cancer trials, of which more than 750 were actively recruiting. Narrowing such a list to *relevant* trials based on diagnosis, location, disease

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progression, and treatment history is currently beyond the average patient's ability and many clinicians. Developing online search tools that meet the needs and expectations of patients and clinicians will require consumer-grade user interfaces and 21st Century data structures, the participation and support of all stakeholders—patients, clinicians, researchers, clinical trials staffs, industry, government, and advocacy—and sufficient budget, staffing, and time.

Trials from the patient perspective—Treatment? Or experiment?

The path to new treatments is paved by willing volunteers who take a chance on new treatment options presented with equipoise by clinicians. As researchers have questions, patients seek answers and solutions. They begin by defining what a specific trial means to them. This starts with a fundamental question that must be answered from the patient's perspective: is this trial a treatment—or an experiment?

In the case of nontherapeutic trials (e.g., SWOG S1314 [6]), the answer is clearly experiment—no treatment is being offered that will benefit that specific patient. From the patient's perspective, nontherapeutic trials are experiments—and not treatments.

Although it is always important for the patient to understand the full scope of the study (treatment where applicable PLUS translational science, quality of life, and other correlatives), it is particularly important when the patient will not *personally* benefit. Although these trials offer low reward and sometimes, but not always, low risk, we are fortunate that many patients are willing to participate. Without them, we cannot deliver future trials that leverage findings from experimental trials and answer our fundamental question with "both"—experiment and treatment.

Trials that do offer treatments should deliver substantive benefits to patients and not just researchers. Individual patients can then determine whether the differences are meaningful enough.

In most cases, the trial is both experiment and treatment. After all, clinical trials are not conducted with the answer already known—that is why they are done. Many patients do not understand that randomized trials are designed to answer questions. As a result, patients have inappropriate expectations of trials and expect better outcomes [7,8]. Many will believe that newer is better or that an answer really exists already and the trial is merely validation. Some will mistakenly believe that no other treatment is available to treat their condition. A patient with an advanced cancer will often believe that a trial will somehow lead to a better future or even a cure [9]. Therefore, setting clear expectations with patients about their outcomes from this trial is both fundamental and ethical.

Patients at the center: What patients want

Having resolved the question of experiment or treatment, patients can think about the trial from other important perspectives, starting with the theoretical effect on quantity and quality of life. What could potentially happen to the patient on each arm of the trial is an important factor in a patient's decision-making process, and discussion must be candid and robust. Additional testing or treatments must be clarified. Side effects must be weighed against potential benefits, with probabilities for any individual patient murky at best. Both patient and caregiver should be alerted to early warning signs of side effects and negative responses to trial treatment along with mitigation plans. The caregiver role in reporting outcomes early must be emphasized to ensure that impacts are minimized. Trust is critical here, particularly in the genitourinary realm, where deeply personal outcomes such as changes in sexual function, continence, and fertility preservation could result.

Informed consent documents are intended to present all relevant outcomes and considerations, including side effects, at an appropriate level of health literacy and completeness. Typically, they miss the mark [10]. Few patients will adequately understand the informed consent document without assistance from medical staff; many will be intimidated by it. And it is only getting tougher for patients as informed consents continue to become more complex [10,11]. Patients need time to understand the form, particularly those who are receiving their diagnosis at the same time. In light of this, it is probably not best practice to introduce a trial and have the patient consent that same day, though practical considerations like transportation and scheduling must be considered. For many patients, family input is important [12]. Trial coordinators and staff are important participants in the process, but physician influence is a key influencer of trial participation [13] and patients strongly prefer communication from their physician. The physician must complete the process believing that the patient and all decision-makers understand the trial after consenting, and doing so requires active oversight of the consent process.

Trials that include a placebo arm trigger a particularly challenging discussion, not surprising given that 57% of patients in a recent survey expressed fear they would receive a placebo [14]. Patients also have misconceptions about placebo, with some believing that standard of care is withheld in placebo trials [15]. Patients understandably have a bias for action, and the inclusion of a placebo belies that principle. Patients offered a trial with placebo face the outcomes of inaction on that arm—disease progression and related consequences. Not surprisingly, these patients often seek alternatives and this becomes more likely as time passes. In addition, placebo administration often includes logistical and financial burden such as time away from work, childcare or elder care, travel to and from the institution, parking, down time waiting for treatment to start and end, etc. This is time—and often money—for the patient. These considerations can make a placebo trial much less appealing to a patient and more likely to trigger concerns and questions.

Use of crossover to the nonplacebo treatment and randomizations that favor it (e.g., 60/40 randomizations in 2 arm trials) can be effective in mitigating the use of placebo. Patients want better odds for a perceived positive outcome,

which these mechanisms deliver. Additionally, patients that are offered standard of care or standard of care plus placebo in the control arm will be more inclined to participate if both arms deliver oncologic benefit. Short of that, in a perfect, patient-centric world, patients would be given the opportunity to select the arm of the trial in which they participate. This would help reduce the discomfort that an estimated 61% of survey respondents have being randomized to a treatment arm [16]. However, such "patient preference trial designs" [17–20] are not commonly used. They are most relevant where blinding is difficult, the patient volunteer will have strong preference for a treatment or where compliance to one or more arms may be a concern. Patient preference designs require sophisticated statistical methods and careful oversight to ensure that the methodology is appropriate and results will ultimately be meaningful.

Trials where the tumor is not removed may conflict with patient's bias for action and mistaken belief that the tumor is the cancer in its entirety. Consequently, it is important for clinicians to carefully educate the patient on the rationale for any tumor retention and provide compelling evidence of the advantages.

The patient should always be provided accurate, complete, and culturally competent [21,22] information before making a decision, and this may require that the patient seek a second opinion, if for no other reason than to validate information provided by the trial recommender. The increasingly rapid rate of drug development reinforces the need for additional input and a thorough scan for available trials. This need will likely continue and potentially increase over the course of the clinical trial and the disease. Patients often have regrets as they navigate their cancer journey, but getting a second opinion is typically not one of them.

Beyond the medical inputs, logistical burdens must be calculated and absorbed, often in collaboration with family and friends. Given that trials are typically more prevalent in urban settings, many patients will find that distance is a challenging if not insurmountable obstacle (18% in the Cancer Support Community survey thought that logistical barriers such as transportation would make it impossible to fulfill trial requirements [23]).

Patients with the option of participating in a trial also face the associated financial burden, with a dizzying array of copayments, coinsurance, deductibles, child/elder care, transportation, lodging, and other out-of-pocket expenses requiring estimates if the patient is to consider them in the decision-making process. Sadly, an estimated 24% believed their insurance would not cover clinical trial costs [24]. In fact, patients typically have insurance coverage for standard-of-care items on a clinical trial, though it is not 100% coverage given copayments, coinsurance, and deductibles. Out-of-pocket expenses are also not covered, and can be substantial for trials with significant logistical burden. Funding for items required by the study but not standard of care may be covered by the study. Most patients are blind to costs before they are billed, and even the medically savvy will most certainly find themselves unable to forecast.

The most recent data on participation in NCI clinical trials [25], published in 2003, revealed direct costs for treatment for nonpediatric trial participants were on average 6.5% higher, totaling an estimated $16 million in 1999 for NCI-sponsored trials. The changing landscape of health care insurance coupled with indirect costs borne by the patient (child/elder care, transportation, lodging, etc.), which were omitted from this study suggest a refresh with an expanded scope would be warranted.

Given that 57% of Americans have less than $1,000 in savings [26], it is no surprise that financial burden and financial toxicity are receiving greater attention from patients and advocacy groups. Regardless of the patient's perceived financial and insurance status, the topic of financial considerations should be part of comprehensive cancer care and discussed proactively. Today, these conversations are estimated to occur only between 14% and 19% of the time in the oncology setting [27,28].

The patient is clearly making trade-offs across somewhat predictable dimensions that are always extremely personal. Navigating those trade-offs is tremendously challenging, and the patient, clinician, and medical staff in a comprehensive care setting will struggle to find time to address all concerns. Connecting a patient with peer support is a good practice accepted by multiple physician groups. The patient can get detailed information and a patient perspective that a busy clinician cannot always provide. Advocacy groups and peer support have evolved and should now be considered extensions of the care team.

Finally, the patient must have the right expectations of the trial [29]. Too many patients have unrealistic goals about treatment in general [30], and the clinical trial context must balance productive optimism with statistical truths. The patient should understand if the treatment can cure, delay or slow the disease or improve quality of life. As part of that conversation, advanced care planning, financial planning, medical directives, and palliative care should all be discussed early, clarifying that such discussions do not necessarily reflect the expectation of a bad outcome.

Discussing trials: Shared decision-making (SDM)

The decision to participate in a clinical trial is difficult and may be the most important decision that patients ever make, not just about their treatment but perhaps in their lives. Inputs into that decision have been described above, but these are only some of the criteria and each patient will weight them differently. The clinician's role in this process is critical and the clinician's goal should be to become a trusted partner to the patient and caregiver and enable shared decision-making (SDM). Anything less can result in an uninformed decision on the patient's part. New clinical guidelines are emphasizing SDM in all phases of patient

care (e.g., AUA/ASTRO/SUO Clinically Localized Prostate Cancer guidelines) [31].

Discussions about clinical trials should be honest, comprehensive, and neutral. Equipoise is critical throughout the process, and the patient may seek answers that are not available. Saying "I don't know" or "We don't know" can be appropriate. Discussion should be collaborative, and the patient must leave having been an integral part of a shared decision-making process. This requires communicating information at a patient-friendly level and asking questions to ensure comprehension. Some will have just received their diagnosis—potentially unexpected, typically devastating and overwhelming—and this will make comprehension that much more difficult.

Two undercurrents to any discussion with the patient about clinical trials must be acknowledged. The first is that the low awareness of trials requires general education about trials to be integrated into the discussion [32]. Patients need to understand enough about clinical trials to decide on the specific trial being discussed—but not so much that the core messaging is lost. Second, patients aware of clinical trials bring preconceived notions, including the common misconception that trials are the last desperate hope of patients who are dying. Those trials which address less advanced statuses will suffer under this fallacy.

Closing the loop: Communicating trial results

Patients participate in clinical trials for many reasons. Fundamentally, participation hinges on a belief that something better is available for that patient or those that will follow [33]. Patients want to know that their participation and that of others has enabled medicine to move forward even if the standard of care does not. This expectation is true whether the trial has a positive result or not.

Although personal debriefs are ideal and perceived by patients as needed [33], they are not always possible. When delivering results to patients or the community at large, results should be presented in a patient-friendly manner. By communicating results, the sacrifices and risks of clinical trial volunteers are honored, the implicit contract between patients and researcher is completed, and future patients, clinicians, and researchers have a clearer understanding of these new findings.

Conclusion

The bar that defines success for cancer clinical trials has been raised with accelerated discovery options and increasing patient-centricity. With the latter comes an understanding of a broader set of criteria which patients use to make decisions. By viewing the challenges and opportunities from the patient perspective, researchers can design and staffs can implement trials that ask questions that are meaningful to patients and tip the balance of risk reward as perceived by patients more heavily to reward. Clinical trial participation will increase, fewer trials will close due to lack of patient participation, and sponsors will be willing to fund more of them.

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