

How important are willingness to participate studies in encouraging patient enrollment in oncology trials?

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Despite the 3.5% increase in the FY2014 National Institutes of Health budget compared with the previous cycle [1], the recent budget sequestration and increasing funding uncertainty for clinical trials underscores the importance of optimizing the design of cancer clinical trials to ensure successful completion, including *a priori* evaluation of strategies to maximize patient accrual. Currently, only half of National Cancer Institute (NCI) Cooperative Group trials are completed. Several factors contribute to the limited success rate of these trials, including poor study designs, insufficient funding, and regulatory hurdles. Despite a first-rate US health care system that has the greatest number of available oncology clinical trials, it is disappointing that only 3–5% of adults enroll in clinical trials [2].

The potential for both selective enrollment and underenrollment is increasingly cited by scientific review committees in questioning the feasibility of proposed trials, which is not surprising since cancer clinical trials are becoming increasingly complex, often combining multiple treatment modalities, employing targeted therapies, and having more radiology and biologic correlative studies. Nearly a decade ago, Halpern proposed prospective preference assessment (PPA) as a method to improve patient enrollment and identify subgroups of patients who may benefit from a potential trial [3]. With PPA, potential subjects are interviewed using five key components: presentation of a hypothetical trial resembling the planned trial, assess-

ment of the patient's understanding of the study design, open-ended questioning to assess motivations for and concerned about the planned trial, written questionnaires to evaluate patient's stated willingness to participate in the planned trial, and assessment of their willingness to participate when one or more identified important factors is varied [3].

We recently used PPA to conduct the first series of studies of patients' willingness to participate in radiation oncology trials. In 2011, our group performed a PPA of patients' willingness to participate in a randomized control trial of proton beam therapy versus intensity-modulated radiotherapy for localized prostate cancer. We undertook this study because of the high cost of the two proposed treatment arms, as well as the potential for strong patient preferences for one treatment versus the other, both of which contributed to our uncertainty regarding the feasibility of the proposed trial. In our study, we prospectively enrolled and interviewed 46 patients using purposeful sampling to ensure a diverse sample based on travel distance, age, race and physician provider. Using semi-structured interviews, we presented patients with a hypothetical trial description and asked several open-ended and focused follow-up questions regarding both their motivations for and concerns about trial enrollment. Using qualitative research analytic techniques, we identified over 20 factors that impacted patients' willingness to participate in the proposed randomized

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prostate cancer trial, including concerns about randomization, time demands, altruism, desire to compare treatments, financial incentives, and deference to the opinion of their physician. Most patients (59%) stated that they would “definitely” or “probably” participate [4]. With these encouraging and informative results, it was determined that conducting the randomized trial would be feasible, and the factors identified in the willingness to participate study were subsequently used to develop and refine the study protocol to better ensure high levels of patient accrual and participation.

Most recently, we used qualitative research methodology to evaluate patients’ willingness to participate in a randomized controlled trial of radical pleurectomy with or without intraoperative photodynamic therapy for malignant pleural mesothelioma. We conducted this rigorous assessment of patient-centered factors to attempt to better inform the feasibility of our proposed clinical trial since malignant pleural mesothelioma is a rare disease and the experimental arm of the proposed trial dictates an invasive treatment modality of photodynamic therapy with unique added toxicities but significant potential benefits of sterilizing microscopic residual disease after gross macroscopic resection. Analysis of this willingness to participate study will inform the feasibility of the proposed trial and may serve to maximize accrual.

There remains much work to be done to decrease barriers to clinical trial enrollment, especially as it pertains to enrolling under-represented groups, such as women and racial and ethnic minorities who remain significantly less likely than non-Hispanic white oncology patients to enroll in clinical trials [5,6]. Ellis and colleagues conducted a cross-sectional survey of 545 women at a breast clinic. They found that women were more likely to participate in a randomized control trial if they had knowledge of its methodology [7]. Shavers and colleagues examined factors that influence African-Americans’ willingness to participate in biomedical research. Using mail and telephone surveys, the investigators collected data from 91 African-American residents of the greater Detroit (MI, USA) area. They found that patients were less willing to participate if they gave importance to their physician’s race, believed that they will take on most of the study risks, or had prior knowledge of the Tuskegee syphilis study [8].

Although Latin Americans comprise nearly 20% of the US population [9], they represent only 2–3% of cancer clinical trial participants. As such, there is a paucity of information regarding factors important for clinical trial awareness in this population. In

a recent cross-sectional survey of Latin Americans, only 48% of participants had knowledge of clinical trials. Interestingly, after being educated on the concept of a clinical trial, an impressive 65% expressed a willingness to participate. The investigators found that, although providers are a vital source of health information for Latin American patients, providers were not associated with patients’ knowledge of clinical trials or desire to participate [10].

Currently, many patients with cancer believe their needs to obtain information about their disease and about clinical trials from their healthcare providers are unmet [5]. An innovative effort to combat this was the multicenter, Phase III Preparatory Education About Clinical Trials (PRE-ACT), which was presented at the 2013 Annual Meeting of the American Society of Clinical Oncology by Meropol and colleagues [11]. Using an interactive Web-based platform prior to patients’ oncologic visits, 1255 patients were randomized to either PRE-ACT, short educational videos in direct response to stated concerns about trial participation or generic written information about trials from the NCI. Although patients in both study arms expressed greater knowledge of clinical trials following the allocated intervention, patients in the PRE-ACT group demonstrated significantly decreased attitudinal barriers and increased knowledge of clinical trials, underscoring the importance of proactively addressing each potential participant’s unique concerns. Providing additional information about clinical trials can lead to better-informed patients, which could translate into increased trial participation. It remains to be seen, however, whether the PRE-ACT trial findings will result in actual improvement in clinical trial participation.

Moving forward, it is imperative that healthcare providers provide patients with individualized, tailored information as they consider participation in cancer clinical trials. Willingness to participate studies using methodology such as PPA should be considered prior to activating oncology clinical trials, especially for orphan malignancies for which trial accrual could be challenging and study limiting.

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