Consent Timing and Experience: Modifiable Factors That May Influence Interest in Clinical Research

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Abstract

Purpose: Low rates of participation in cancer clinical trials have been attributed to patient, institutional, and study characteristics. However, few studies have examined factors related to the consent process. We therefore evaluated the impact of consent timing and experience on markers of patient interest in research.

Methods: We performed a retrospective analysis of patients enrolled in a cancer center tissue repository. During enrollment, patients were asked if they were willing to be contacted in the future to provide medical follow-up information and/or to participate in other clinical research. We analyzed the association between patient responses to these questions and consent process factors using univariate analysis and multivariate logistic regression.

Results: Of 922 patients evaluated, 85% agreed to be contacted to provide follow-up information, and 83% agreed to be contacted to participate in future research studies. In univariate analysis, willingness to be contacted for future research was associated with consenter experience ($P = .01$) and had a trend toward association with the timing of enrollment in relation to diagnosis ($P = .08$), but it was not associated with patient sex, race, or diagnosis. In multivariate analysis, responses remained associated with consenter experience ($P = .02$).

Conclusion: Factors related to the consent process, including consenter experience and timing of study enrollment, are significantly associated with or have a trend toward association with markers of patient interest in clinical research. These understudied and potentially modifiable variables warrant further evaluation.

Introduction

Only 1% to 3% of adult patients with cancer in the United States enroll onto clinical trials.[1-4] This low participation rate hinders clinical advances and limits research generalizability. Accordingly, much effort has been devoted to identifying the variables that limit and facilitate clinical trial accrual. Cited factors include patient characteristics such as age,[5,6] sex,[3] race,[7-9] and socioeconomic status[7,10,11]; institutional factors such as clinical trial availability[4,9]; and study factors such as eligibility criteria.[12]

However, relatively little research has focused on the role of the consent process in clinical trial participation. Using a university-based tissue repository, we previously evaluated the impact of consenter characteristics on participant interest in clinical research.[13] Specifically, we used the surrogate end point of patients' agreeing to be contacted for future research studies. In that study, willingness to be contacted for future research was associated with the total number of participants consented by an individual consenter and with participant-consenter sex discordance. In the present study, we analyze the associations between consent timing, experience, and markers of patient interest in clinical research. We chose to focus on these variables because, in contrast to inherent patient characteristics and study eligibility criteria, they represent factors in the research process that might be readily modified.

Methods

Data Source and Research Setting

The University of Texas Southwestern (UT Southwestern) Tissue Resource is a university-based tissue repository. Since its inception in 2000, the tissue resource has stored tissue and blood samples from consenting participants undergoing a biopsy or surgical procedure for suspected or confirmed cancer. Tissue and/or blood samples, along with corresponding clinical data, are collected and archived prospectively for future research studies. Participants enrolling in the tissue resource are asked the following two questions on the consent form: one, "May members of the University of Texas Southwestern Medical Center Tissue Resource contact you in the future for follow-up information?" and two, "May members of the University of Texas Southwestern Medical Center Tissue Resource contact you in the future to ask you to take part in more research?" Participation in the tissue resource is not dependent on responses to these questions. The consent form is available in both English and Spanish, and participants who speak other languages are enrolled through use of a short-form and translator.

Participants in the UT Southwestern Tissue Resource are recruited from various clinical facilities affiliated with UT Southwestern. These include Parkland Health and Hospital System (968-bed county safety-net hospital and associated outpatient clinics), University Hospital (415-bed tertiary care, inpatient facility), and the Harold C. Simmons Cancer Center, a freestanding National Cancer Center–designated outpatient facility.

Data Collection

This study was approved by the UT Southwestern institutional review board. For each of the patients enrolled in the UT Southwestern Tissue Resource, we obtained the following data: age, sex, race, diagnosis, and responses to questions one and two

listed on the consent form. Date of disease diagnosis, date of enrollment in the tissue resource, and identity of the individual who enrolled the patient were also obtained.

Patient race was characterized as non-Hispanic white or other. Race was dichotomized to increase the statistical power of the analysis; in our earlier study of research interest, we found no association when race was characterized as non-Hispanic white, Hispanic, African American, or other.[13] Diagnosis was characterized as cancer, benign, or healthy control (generally a family member of a patient in the tissue resource who agreed to provide a blood sample for tissue resource). Timing of enrollment was defined as the interval between date of diagnosis and date of enrollment in the tissue resource. Healthy controls (n = 43; 4% of total participants) were not included in this analysis, because they did not have a date of diagnosis. Consenter identity and date of enrollment were used to determine the order in which patients were enrolled in the tissue resource by individual consenters, which was used as a marker of consenter experience.

Table 1. Baseline Patient Characteristics (N = 922)

Characteristic	No.	%
Age, years		
≤ 65	691	75
> 65	231	25
Sex		
Male	305	33
Female	617	67
Race		
White (non-Hispanic)	578	63
Other	326	35
Unknown	18	2
Disease status		
Cancer	763	83
Benign	116	13
Healthy control	43	4

Statistical Analyses

Patient responses to questions one and two were analyzed separately. In the univariate analysis, we used the Pearson χ^2 test to calculate *P* values. We obtained odds ratios and 95% CIs from the univariate logistic regression. Enrollment order and timing of enrollment were divided into best-fit quartiles. We fitted a multivariate logistic regression model, including the covariates of dichotomized patient age, sex, enrollment timing, and enrollment order. All reported *P* values are two sided. All statistical analyses were implemented by SAS 9.1 for Windows (SAS Institute, Cary, NC).

Results

From June 2000 to September 2007, 922 participants were enrolled in the UT Southwestern Tissue Resource. Baseline patient characteristics are listed in Table 1. As previously described,[13] 67% of patients were female, 75% were age 65 years or younger, and 63% were non-Hispanic white. Enrollment order was determined for 872 patients (95%), who were enrolled by a total of 187 consenters. Among these patients, 187 (21%) were the first patient enrolled by an individual consenter, 186 (21%) were the second or third patient enrolled by an individual consenter, 239 (28%) were the fourth to ninth patient enrolled by an individual consenter, and 260 (30%) were the tenth or later patient enrolled by an individual consenter. The timing of tissue resource enrollment in relation to the date of diagnosis was determined for 899 patients: 217 (24%) were enrolled before diagnosis (typically on day of initial diagnostic procedure), 189 (21%) were enrolled within 1 to 30 days of diagnosis, 239 were enrolled within 31 to 90 days of diagnosis, and 254 (28%) were enrolled more than 90 days after diagnosis.

The majority of patients agreed to be contacted in the future to provide medical follow-up (question one; 84.9%; 95% CI, 82.5% to 87.2%) and to participate in other research studies (question two; 83.1%; 95% CI, 80.6% to 85.5%). Responses to these questions were highly correlated, with 96% of patients responding either "yes" or "no" to both questions ($P < .001$).

Table 2 summarizes the association between patient characteristics and responses in univariate analysis. Patient age was significantly associated with willingness to be contacted for medical follow-up. Among patients age 65 years or younger, 86% agreed, compared with 80% of patients age older than 65 years ($P = .03$). There was a nonsignificant association between patient age and willingness to be contacted for future research (84% *v* 80%; $P = .14$). Patient sex, race, and diagnosis were not associated with responses.

Consenter experience, defined as the order in which a patient was enrolled by an individual consenter, was significantly associated with willingness to provide medical follow-up ($P = .024$) and to be contacted for future research studies ($P = .01$; Figure 1). Among individuals who were the first enrolled by an individual consenter for the tissue resource, 81% agreed to be contacted for follow-up, compared with 84% of patients who were the second or third enrolled ($P = .35$), and 90% of patients who were enrolled tenth or later ($P = .004$). Regarding contact for future research studies, 76% of patients who were the first enrolled by an individual consenter for the tissue resource agreed, compared with 84% of patients who were the second or third enrolled ($P = .06$), and 88% of patients who were the tenth or later enrolled ($P < .001$).

The interval between patient diagnosis and enrollment in the tissue resource was associated with willingness to be contacted for medical follow-up ($P = .04$) and exhibited a trend toward association with willingness to be contacted for future research studies ($P = .08$; Figure 2). In both instances, willingness to be contacted was greatest 1 to 30 days after diagnosis. For medical follow-up, 90% of patients enrolled during this time period replied "yes," compared with 84% of patients enrolled before diagnosis ($P = .07$). "Yes" responses then declined over time to 80% for those patients enrolled more than 90 days after diagnosis. Similarly, agreement to be contacted for future research studies was greater among

Table 2. Univariate Analysis of Association Between Patient and Disease Characteristics and Patient Responses

	Medical Follow-Up							Future Research						
	"Yes"		"No"					"Yes"		"No"				
Characteristic	No.	%	No.	%	OR*	95% CI	*P*	No.	%	No.	%	OR*	95% CI	*P*
Age, years							.03							.14
≤ 65	580	86	92	14	Ref			585	84	107	16	Ref		
> 65	178	80	44	20	0.64	0.43 to 0.95		177	80	45	20	0.75	0.51 to 1.10	
Sex							.19							.31
Female	521	86	85	14	Ref			509	84	97	16	Ref		
Male	242	83	51	17	0.77	0.53 to 1.13		238	81	55	19	0.83	0.57 to 1.12	
Race							.83							.40
White†	486	85	85	15	Ref			479	84	92	16	Ref		
Other	263	85	48	15	0.96	0.65 to 1.41		254	82	57	18	0.86	0.60 to 1.23	
Disease							.90							.30
Cancer	627	85	114	15	Ref			612	83	129	17	Ref		
Benign	99	86	16	14	1.13	0.64 to 1.98		101	88	14	12	1.52	0.84 to 2.74	
Healthy control	37	86	6	14	1.12	0.46 to 2.72		34	79	9	21	0.80	0.37 to 1.70	

Abbreviations: OR, odds ratio; Ref, reference.
* OR > 1: more likely to answer "yes."
† Non-Hispanic.

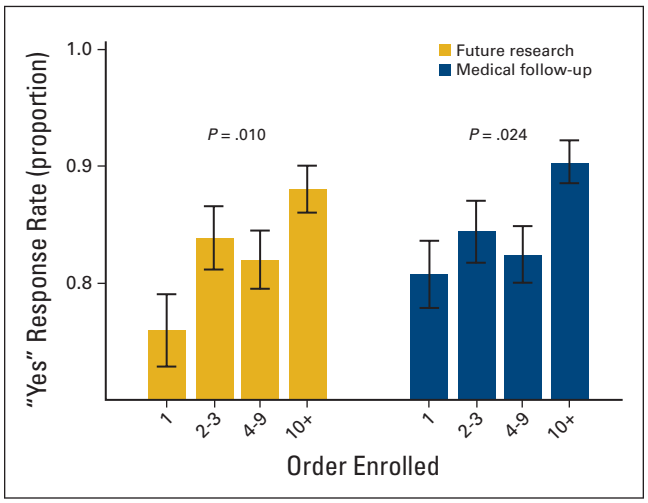

Figure 1. Association between order of enrollment and patient response.

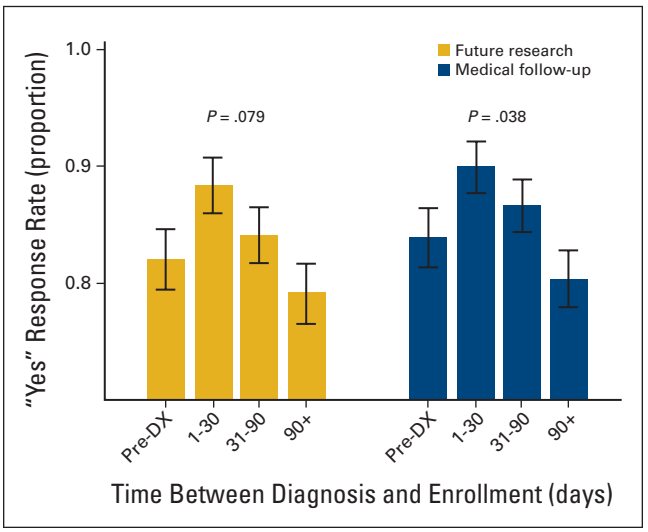

Figure 2. Association between timing of enrollment and patient response. DX, diagnosis.

those patients enrolled in the tissue resource 1 to 30 days after diagnosis than among patients enrolled before diagnosis (88% *v* 82%; $P = .08$). Among patients enrolled in the tissue resource more than 90 days after diagnosis, 79% agreed to be contacted for future research.

In multivariate analysis (Appendix Table A1, online only), the order in which a patient was enrolled by an individual consenter remained associated with patient willingness to be contacted for medical follow-up information ($P = .01$) and future research ($P = .008$). Age was significantly associated with willingness to be contacted for medical follow-up ($P = .01$) and exhibited a trend toward association with willingness to be contacted for future research ($P = .08$).

Discussion

The impact of patient, institutional, and study factors on cancer clinical trial accrual has been examined extensively, but few studies have investigated whether patient interest and participation in clinical research vary by aspects of the research consent process. In this study of patients enrolled in a cancer center tissue repository, we focused on two such potentially modifiable factors: consenter experience and timing of consent. We found that consenter experience was significantly associated with and timing of consent had a clear trend toward association with markers of patient interest in research.

We categorized consenter experience according to the number of participants enrolled in the tissue repository by an indi-

vidual consenter. Among patients enrolled by first-time consenters, 76% agreed to be contacted in the future to participate in other research studies, compared with 84% of patients who were the second or third participant enrolled by an individual consenter, and 88% of patients who were the tenth or later participant ($P = .002$). Considered conversely, the proportion of patients declining future contact went from 24% to 12%, a 50% relative decrease.

These results build on our previous work, in which we found that participants enrolled by high-volume consenters were more likely to agree to be contacted for medical follow-up and future research studies.[13] In that study, participants consented at any point by study personnel who ultimately enrolled more than the median number of participants per consenter (ie, eight) were more willing to be contacted for future research. With this earlier approach, however, many participants enrolled by an experienced consenter were enrolled at a point when that consenter was not yet experienced, suggesting that other consenter characteristics—such as interest in and enthusiasm for the study—may have contributed to participant response. By examining the specific order in which a patient was enrolled by an individual consenter, the present study provides a more clinically relevant and applicable measure of consenter experience.

Along these lines, prior research has suggested that a supportive and clear physician communication style is associated with patient and family interest in clinical research.[14] It has also been shown that direct interaction between study personnel and participants is the most effective means of improving participants' understanding of information disclosed in the informed consent process.[15] Other studies have demonstrated that interventions such as workshops and videos can improve research personnel communication skills[16-19] and quality of informed consent[20] in cancer clinical trials. In the present study, however, consenter experience more likely reflected familiarity with study-specific content and documents than it did general communication skills. First, our data do not account for consenter experience with other research protocols. For some consenters, the first participant enrolled in the tissue resource may have been the first participant he or she enrolled on any research study, whereas others may have participated in numerous prior clinical trials. Second, it is unlikely that consenters' general communication styles would have changed significantly after enrollment of a single participant in the tissue resource.

As clinical research becomes more complex, this ability of research personnel to understand and explain study-specific details and consent documents is likely to become even more important. Over time, consent forms have become longer[21,22] and more difficult to comprehend.[23,24] The consent form for the UT Southwestern Tissue Resource, the basis of the present study, provides a relevant example. Although study procedures are straightforward—namely, the procurement and storage of clinical information and excess tissue from a procedure performed as standard clinical care—the six-page document covers such complex concepts as compensation for injury, compensation for future commercial developments, and the definition, processing, and storage of DNA.

We also evaluated the timing between diagnosis and invitation to participate in the research study—a factor in the research consent process that has not, to our knowledge, been evaluated previously. Willingness to be contacted for medical follow-up and future research studies was greatest among those patients enrolled between 1 and 30 days after disease diagnosis. A potential explanation is that this interval features less uncertainty and anxiety than the prediagnosis period, during which patients may be more focused on the risks and results of the upcoming diagnostic procedure than on the possibility of future research participation. Furthermore, the early interval after diagnosis is established may represent the height of patients' interest in their disease and treatment, as evidenced by a consistent and significant decline in willingness to be contacted for medical follow-up and future research among patients consented after this period. This observation has particular relevance to those clinical trials, such as secondary prevention studies, that require a waiting period of several months after initial cancer diagnosis and treatment before enrollment.

In this study, patient characteristics predicted responses to a lesser degree than did factors related to the consent process. Willingness to be contacted for medical follow-up and future research was not associated with sex ($P = .19$ and $P = .31$, respectively) or race ($P = .83$ and $P = .40$, respectively). Numerous studies have demonstrated racial disparities in clinical trial accrual[7-9]; our results suggest that these differences may in part reflect access to trials or reservations about specific study procedures,[25] rather than a general aversion to clinical research. Consistent with previous reports,[26,27] older patients in this cohort seemed less willing to be recruited for future research studies.

This study has a number of limitations. Foremost among them is the nature of the primary end point. It is not known if willingness to be contacted for future research opportunities correlates with willingness to participate in research, whether therapeutic or observational. Agreeing to be contacted for future research opportunities is clearly not equivalent to enrolling onto a clinical trial. The former entails minimal commitment or risk, whereas the latter may directly affect treatment selection, toxicities, and clinical outcomes. Nevertheless, patient willingness to consider clinical research represents a critical element of study accrual. We also believe this end point to be more interpretable than clinical trial enrollment, which depends not only on patient preference, but also on external factors such as study eligibility and availability. Although statistically significant, the different results between less and more experienced consenters may on initial consideration seem not clinically meaningful. Indeed, additional experience yielded a relative increase in "yes" responses of only 16%. This result reflects the high baseline rate of agreement to be contacted for future research, which leaves little room for improvement. However, applying the 50% relative decrease in "no" responses we observed to a hypothetical but plausible research scenario in which—perhaps because of difficulties in understanding more complex study content and procedures—a smaller proportion of potential participants agree to participate at baseline, the effects could be substantial.

In addition, aspects of the study population may limit the generalizability of our findings. In our study setting—an academic medical center—patients, staff, and clinicians may have research interests and motivations distinct from those encountered in community practices. This setting may also account for the atypically young age of the study sample (75% ≤ age 65 years), which in turn could bias our results. The 17% of participants who had either benign disease or were healthy controls may have skewed our findings, although disease status was not significantly associated with participant responses in univariate analysis. Finally, the study cohort included only those patients who agreed to participate in the UT Southwestern Tissue Resource. We have no information on those who were never approached to participate in the tissue resource and only limited information on those who were approached but declined. However, we believe our cohort is at least as representative a patient sample as those included in survey- or questionnaire-based studies, in which response rates are generally only 20% to 30%,[28,29] and participants may be particularly motivated and interested in research. By contrast, because the UT Southwestern Tissue Resource entails little risk or time commitment, the overwhelming majority of those approached agree to participate. As a result of our interest in this issue, the UT Southwestern Tissue Resource recently started recording these figures; since that time, 514 (92%) of 556 individuals approached have agreed to enroll.

In conclusion, this study demonstrates that factors related to the consent process may affect patient interest in and willingness to consider participation in clinical research. To our knowledge, this is the first study to evaluate these variables quantitatively. Specifically, we found that consenter experience was significantly associated with and timing of consent had a trend toward association with markers of patient interest in research. Consenter experience may be gained as early as the first consenting effort for a particular trial. This experience seems to be study specific and likely reflects familiarity with study procedures and documents. Patients seem most open to the possibility of clinical research shortly after diagnosis, specifically within 30 days. One possible explanation is that before diagnosis, patients are preoccupied by anxiety related to the risks and results of upcoming procedures; as time elapses after diagnosis, patients' interest in their disease and treatment may wane. Patient characteristics including sex, race, and diagnosis were not associated with research interest. Importantly, in this study, the variables most strongly associated with markers of patient interest and potential participation in clinical research—namely, consenter experience and the timing of study enrollment—are readily defined and potentially modifiable. Further study of these factors may improve efforts to increase cancer clinical trial accrual.

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