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Public Health Sciences

**AN ANALYSIS OF RECRUITMENT FOR A NON-TREATMENT BASED
ADVANCE CARE PLANNING RESEARCH STUDY IN TERMINAL CANCER PATIENTS**

A Thesis in

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Abstract

This analysis examines the recruitment for a single-blind randomized controlled study, involving the sensitive topic of advance care planning, the vulnerable population of patients with terminal cancer, and a non-treatment based study intervention. The purpose of this examination was to identify key differences between the groups of patients that enrolled versus those who did not participate, in order to better understand recruitment for this type of study. Statistical analysis of the non-parametric distributions of data identified significant differences in age ($p = 0.021$), distance to study site ($p = 0.010$), race ($p = 0.031$), and number of follow-up phone calls ($p < 0.001$). Gender ($p = 0.88$), referring specialty ($p = 0.076$), and season of referral ($p = 0.22$) were not significantly different. Specifically, non-participants were slightly older, lived farther from the medical center, required more outreach phone calls, and were more likely to report feeling too ill or being un-interested as a reason to not participate. Some barriers to participation were outside of investigators control (i.e. patients who died before contact, were too ill, or unreachable) and represent an inherent inefficiency in recruiting terminally ill participants. The present findings suggest that recruitment efforts can be prioritized to patients who live closest to the study site and towards making initial contact with potential participants.

Table of Contents

List of Tables.....	v
List of Figures.....	vi
Acknowledgments.....	xii
Introduction.....	1
Methods.....	3
Results.....	5
Discussion.....	7
Conclusion.....	10
Tables and Figures.....	11
References.....	16

List of Tables

Table 1: Comparison of Non-Participants and Enrolled Participants Demographics

Table 2: Recruitment Timing Measures

List of Figures

Figure 1: Number of Referrals across Time

Figure 2: Recruitment Protocol

Figure 3: Recruitment Flow

Figure 4: Reason for Declining

Figure 5: Number of Follow-Up Phone Calls

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Introduction

Ethical and efficient recruitment of human research participants is vital to any successful research plan. The study described here used a novel online decision aid to document the end-of-life medical wishes of terminally ill cancer patients, which posed some particular challenges to recruitment. Thru this analysis we can better understand which factors significantly influence the ability to successful recruit patients with life limiting conditions in non-clinical research.

Three major categories of recruitment barriers have been described in the literature: institutional, physician-related, and patient-related (Grunfeld, Zitzelsberger, Coristine, & Aspelund, 2002). Institutional barriers describe the overarching culture of bureaucracy where the research is being conducted. The priorities of each department determine how much time, resources, and rewards will be allotted to conducting research (Tooher, Middleton, & Crowther, 2008). Similarly, physicians acting as “gatekeepers” in an effort to protect their patients may impede efforts to achieve a representative sample (Gurwitz et al., 2001; Steinhauser et al., 2006). Patient-related barriers encompass the divide between those who express interest in research and those who actually consent to participate. Furthermore, patients with precious time and energy experience multiple conflicting priorities, which can further complicate recruitment (Kirchhoff & Kehl, 2007; Phipps et al., 2005; Williams, Shuster, Clay, & Burgio, 2006).

Despite evidence that patients at the end of life are interested and willing to participate in research (Kendall et al., 2007; Shipman et al., 2008; Williams et al., 2006), physicians who care for these patients often regard research as a threat to the fragile wellbeing of these vulnerable patients (Fischer, Burgener, Kavanaugh, Ryan, & Keenan, 2012). In their efforts to protect patients, these physicians are often reluctant to help enroll patients in studies about end of life care, which has the paradoxical effect of hindering advances in our knowledge about what will enhance quality of life during patients final weeks and months. With consideration to the context of institutional barriers to non-therapeutic research, it is

incumbent that we better understand which patient related factors significantly influence the ability to successfully recruit patients with life-limiting conditions.

One pillar of end of life care is the process of Advance care planning (ACP), which facilitates individuals to prepare for future medical care should they lose decision-making capacity; the document that captures these wishes is known as an advance directive. Despite strong evidence in support of ACP (Lautrette et al., 2007; Weiner & Roth, 2006; Wright et al., 2008), most adults do not engage in the process and less than 25% of Americans have completed an advance directive (Hanson & Rodgman, 1996). There are countless complex reasons for these low completion rates (Billings, 2012; Hinders, 2012; McMahan et al., 2013; Moorman, Carr, Kirchhoff, & Hammes, 2012), and such barriers can present significant challenges to enrolling participants into research studies of this sensitive topic of ACP.

Recruitment for non-treatment based studies has not been nearly as well researched as clinical drug and device trials (Advani et al., 2003; Grunfeld et al., 2002; Mills et al., 2014; Wood, Wei, Hampshire, Devine, & Metz, 2006). Enrollment rates for cancer clinical trials average 60% when the focus of the study is to find a cure (Talarico, Chen, & Pazdur, 2004). However the potential for recovery may be the most alluring incentive for participants. Non-therapeutic studies cannot offer the same hopeful motivator (Kleiderman et al., 2012) and therefore, have distinct barriers to recruitment in need of further investigation.

The combination of (1) known challenges to end of life research, (2) with the social taboo associated with advance care planning and (3) the recruitment issues inherent to non-therapeutic trials limited the efficiency of recruitment for this single-blinded randomized controlled study. The central research question examined here is what were the barriers for patient enrollment to this non-treatment based interventional trial, and how can researchers for similar studies anticipate and innovate around such barriers?

Methods

a. Description of Recruitment Protocol

This single-blinded randomized controlled study was conducted at a tertiary academic medical center in central Pennsylvania and funded by the American Cancer Society. Its purpose was to compare two methods of ACP among 200 patients with advanced cancer, in terms their ability to help align patients values and medical wishes with actual end-of-life treatment. Achieving this recruitment required 1,988 referrals over 5 years from 30 physicians in 20 clinics (Figure 1).

The recruitment process (Figure 2) began with approaching physicians, or their designee, on a monthly or bimonthly basis with a list of adult patients that was pre-screened for 1) a qualifying diagnosis of stage IV cancer, and/or 2) a life expectancy less than two years. Providers were then asked if there was “any reason we should NOT contact these individuals” to eliminate those known to have language barriers, cognitive decline, or severe depression. Any patient that the provider felt was appropriate for us to contact was classified as a referral.

Patients were sent a recruitment letter, signed by the referring physician, explaining the project in full detail. An opt-out form was included with a self-addressed stamped envelope to be returned if the patient did not wish to be contacted. If an opt-out form was not received within two weeks, a follow-up phone call was made by the research coordinator to provide an explanation of the study, answer any questions the patient might have, and schedule a study visit if interested. If the patient was not reachable, two additional follow-up reminder calls were made.

Interested patients were scheduled to attend a study visit at which informed consent was elicited and participants were screened for cognitive and language barriers. Exclusion criteria included scoring ≥ 20 on the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), < 23 on the Folstein Mini Mental Status Exam (Folstein, Folstein, & McHugh, 1975), and/or the inability to read through word 26 of the

Wide-Range Achievement Test (Wilkinson, 1993), needed to demonstrate an 8th grade reading level. The eligible patients were then randomized to one of two modalities of ACP: the “Making Your Wishes Known” decision aid(Levi & Green, 2010) or a standard living will form plus an educational brochure. All participants consented were given a \$25 gift card; those not eligible for the study were given the opportunity to complete the “Making Your Wishes Known” decision aid.

b. Analysis of Recruitment

A recruitment spreadsheet was used to track every patient referral to its ultimate endpoint of enrollment or non-participation. This database contained basic contact information including patient name, address, and telephone number. Pertinent recruitment data was also recorded: qualifying diagnosis, date of referral, referring physician, date recruitment letter sent, date of any and all follow-up calls, and enrollment category. If a patient who declined during a phone call provided a reason, it was recorded in the spreadsheet. Demographic data such as date of birth, race, gender and zip code were gathered retrospectively from the electronic medical record.

Using this raw data from the parent study, we calculated participant age at date of referral, distance from home zip code to the study site, number of follow-up phone calls, and time elapsed between recruitment steps. We then compared the group of 200 enrolled patients to the 1,788 non-participants among a number of key variables to illuminate significant differences. Due to their non-normal distribution, a non-parametric Wilcoxon test (aka Mann-Whitney U test) was used to compare patient’s age at referral, elapsed time between recruitment steps, and distance to medical center. A chi-square test was used to compare the categorical variables including gender, race, referring specialist, number of follow-up calls, and season of recruitment.

Results

Of the 1,988 patients referred over a five year period, 200 participants ultimately enrolled; thus ninety percent of the total referrals were classified as non-participants (Figure 3). Among non-participants, 30.5 percent (545/1788) returned opt-out form and 29.6 percent (530/1788) declined participation over the phone. One hundred patients (5.6%) expressed interest but did not follow up before enrollment closed, and 72 (4.0%) did not show for their scheduled appointments and could not be rescheduled. A portion of the 1,788 non-participants were unable to be reached ($n = 217$, 12.1%), 180 (10.0%) were deemed too ill either by the referring physician or the patient themselves, 107 (6.0%) died before contact could be made by mail or phone, and 37 were not eligible (2.0%).

Participants age and commute distance to study site were significantly different between the populations (Table 1), with the non-participants being an average of 2.3 years older ($p = 0.021$) and living a median of 25 miles farther from the medical center ($p = 0.010$). Differences in gender ($p = 0.88$) and referring specialty ($p = 0.076$) were non-significant but a significantly higher portion of non-participants were minorities ($p = 0.031$).

Researchers attempted to contact 1,336 individuals via telephone. Of the 710 individuals who declined participation on the phone or self-reported poor health, 290 reported a reason for declining (see Figure 4). The majority of those who stated a reason reported being too ill (31%, 90/290), or not interested (27%, 78/290). Travel distance (14%, 40/290), lack of time (10%, 29/290), and already having created an advance directive (13%, 38/290) were also mentioned.

Non-participants received significantly more phone calls than those who enrolled ($p < 0.001$). Participants who took the initiative to schedule a study visit after receiving the first recruitment letter (and therefore required no recruitment calls from the research team), were coded as being recruited in zero

phone calls. The number of calls to each participant was tallied to visualize the diminishing return on investment of the project manager's time (Figure 5).

The amount of time that passed from the date of referral to the date the letter was sent did not differ ($p = 0.52$) between participants and non-participants (Table 2). Similarly, the time elapsed from date of referral to first call was not significantly different ($p = 0.22$). Although there was a significantly fewer number of referrals during the winter months ($p < 0.001$), the recruitment rate for referred patients did not significantly differ based on season ($p = 0.22$).

Discussion

The barriers to recruitment we encountered were largely due to the patients' unpredictable illness trajectory, time restraints, and transportation issues. Non-participants were slightly older, lived much farther from the study site, and required more follow-up phone calls. The most commonly reported reasons for declining, feeling too ill or not interested, represent two very different types of barriers from the perspective of the researcher, those completely outside of the researchers control and those that could potentially respond to researcher intervention.

Patients who died before contact, reported feeling too ill, were unreachable or ineligible essentially removed themselves from the referral pool because there is no recruitment innovation that could have led to their enrollment. The unexpected trajectory of terminal illness will always result in some referrals dying before contact and others reporting feeling too ill. Patients who were unreachable or ineligible were referred based on a broad screening process that could not identify a priori the true eligibility characteristics. For example, the majority of patients in the latter category were minorities who were referred knowing they spoke English but then screen failed for not reading at an 8th grade level; this accounts for the significantly fewer enrolled minorities.

A corrected enrollment rate could then be calculated if we remove these 541 inaccessible referrals, from the four categories on the left of Figure 3. The original enrollment rate of 10% becomes a corrected enrollment rate of 14% (200 enrolled out of a 1,447 accessible referrals). This discrepancy between gross enrollment rate and the corrected enrollment rate is an unfortunate inevitable result of erratic illness trajectory and broad screening measures.

In contrast, the patients who returned the opt-out form, declined participation on phone, expressed interest but did not follow-up or did not attend their scheduled appointment may represent an opportunity for recruitment innovation. These patients may have enrolled if researchers adjusted how the study was

presented. For example, the 37 patients that declined to participate due to “already having an advance directive” may have felt differently had the study been explained without overemphasizing this document. These potentially controllable patient barriers, seen on the right of Figure 3, are where researchers can direct their recruitment innovations to see the largest impact.

One such innovation may focus on the distribution of time invested by the recruiting staff. Almost two-thirds of all the enrolled participants were recruited in one or less follow-up phone calls, so there appeared to be a diminishing return on the investment of the project manager’s time. Ultimately only 5% enrolled in four or more phone calls, so recruiters with limited time resources may need to limit follow-up phone calls to three.

Although the number of referrals dropped significantly in the winter, there was no difference seen in enrollment rate based on season. Therefore we saw no reason to adjust the recruitment protocol; time elapsed between the steps in the recruitment protocol remained consistent. Researchers can also innovate by being flexible and accommodating with the patient’s time commitments; 24% of participants who provided a reason for declining to participate reported having transportation issues, or a lack of time. We had some success offering weekend and evening study visits to address participants’ time constraints.

Our results suggest that recruiters with limited time would be wise to prioritize their efforts to patients who live closest to the study site and making initial follow-up contact. Similar studies have used home visits, taxi vouchers, or public transit reimbursement to help participants overcome the perceived transportation barriers (Hanratty et al., 2012; Hunt, Shlomo, & Addington-Hall, 2013; LeBlanc, Lodato, Currow, & Abernethy, 2013), though this was not practical for our more rural environment. A different recruitment letter design that doesn’t overemphasize the AD document may increase the perceived personal benefit (Mills et al., 2006). Lastly, an in-person invitation from the referring doctor (Grinfeld et al., 2002) has also been used in similar studies to address the potentially controllable patient barriers described here.

Like all studies, this one has limitations, including the absence of hard data on the effect of institutional barriers and physician gatekeeping on recruitment. One of the most time consuming aspects of recruitment was developing relationships with the 30 referring providers and maintaining a presence in 20 distinct high-volume oncology clinics. Similarly we did not have a standard method to record the overall proportion of patients with an eligible diagnosis that were not referred by physicians nor the reasoning for why the provider felt the individual referral was inappropriate; we therefore have no way of knowing if the patients who were referred were representative of all eligible patients. Future studies could improve their understanding of recruitment trends by collecting more qualitative data from non-participants, particularly on their reasoning for choosing not to enroll. Relying on the patient to volunteer this information left us with a somewhat cryptic catch-all reason of “not interested,” which may encapsulate a broad range of patient recruitment barriers.

Conclusion

We found that patients who enrolled in an ACP study lived closer to the study site than non-participants. We identified a diminishing return on time investment with multiple recruitment calls since the majority of patients enrolled within the first phone call. Thus, recruiters with limited time should consider prioritizing efforts on patients who live closest to the study site and towards making initial contact with potential participants.

Tables

Table 1: Comparison of Non-Participants and Enrolled Participants Demographics

	Enrolled Participants n=200	Non- Participants n=1788	
	Mean ± Standard Deviation, or Count		p-value
Age	62.0 ± 13.5	64.2 ± 13.1	
Medians	62.6	64.9	0.021^w
Sex			0.88 ^z
Male	107 (54%)	1039 (58%)	
Female	73 (37%)	749 (42%)	
Race			0.031^z
Non-Minority	193 (96%)	1606 (90%)	
Minority	7 (4%)	134 (8%)	
Distance to Med Center	38.4 ± 52.8	50.5 ± 152	
Medians	25.0	50.5	0.010^w
Referring Specialty			0.076 ^z
Hematology Onc	88 (44%)	642 (36%)	
Radiation Onc	42 (21%)	342 (19%)	
Surgical Onc	28 (14%)	364 (20%)	
Neuro-Onc	22 (11%)	251 (14%)	
Other	20 (10%)	188 (11%)	

^w Wilcoxon test, ^z Pearson Chi-Square Test

Table 2: Recruitment Timing Measures

	Enrolled Participants n=200	Non- Participants n=1788	
	Mean ± Standard Deviation, or Count		p-value
Season Letter Sent			0.22 ^x
Dec-Jan-Feb	27 (14%)	231(13%)	
Mar-Apr-May	47 (24%)	514 (29%)	
Jun-Jul-Aug	59 (30%)	556 (31%)	
Sep-Oct-Nov	67 (34%)	488 (27%)	
p-value	<0.001^x	<0.001^x	
Elapsed Time (days)			
From Referral to Letter Sent Medians	3.7 ± 5.6 2.0	4.1 ±7.9 2.0	0.52 ^w
From Referral to First Call Medians	21.9 ± 11.7 20.0	24.3 ± 16.0 20.0	0.22 ^w

^wWilcoxon test, ^xPearson Chi-Square Test

Figures

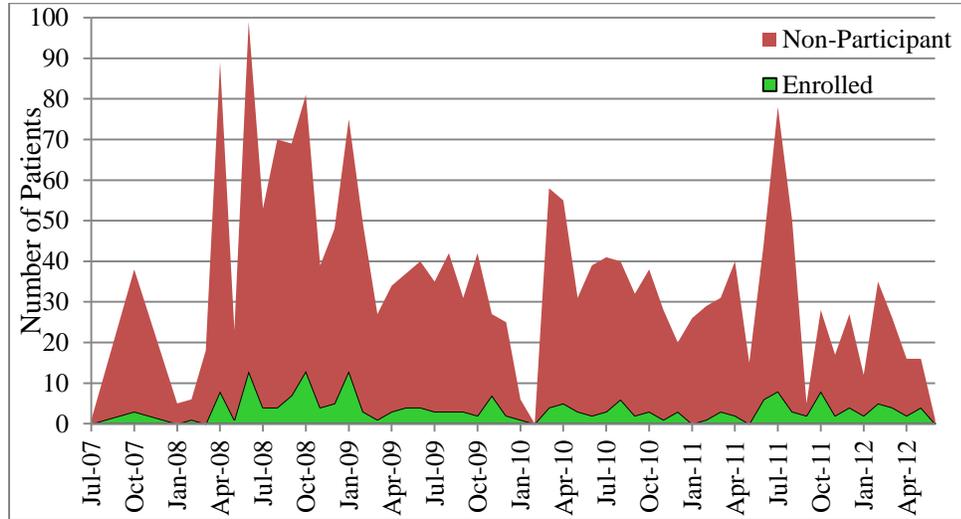


Figure 1: Number of Referrals across Time

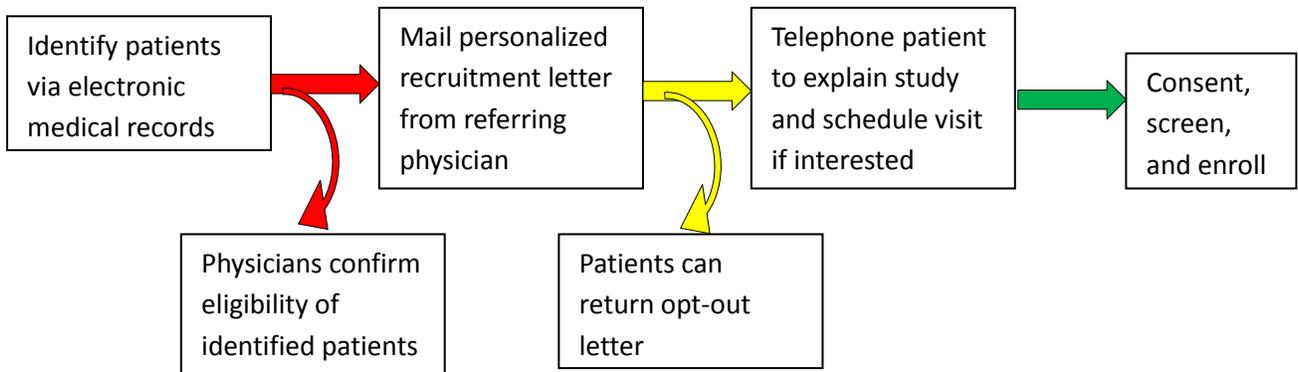


Figure 2: Recruitment Methods

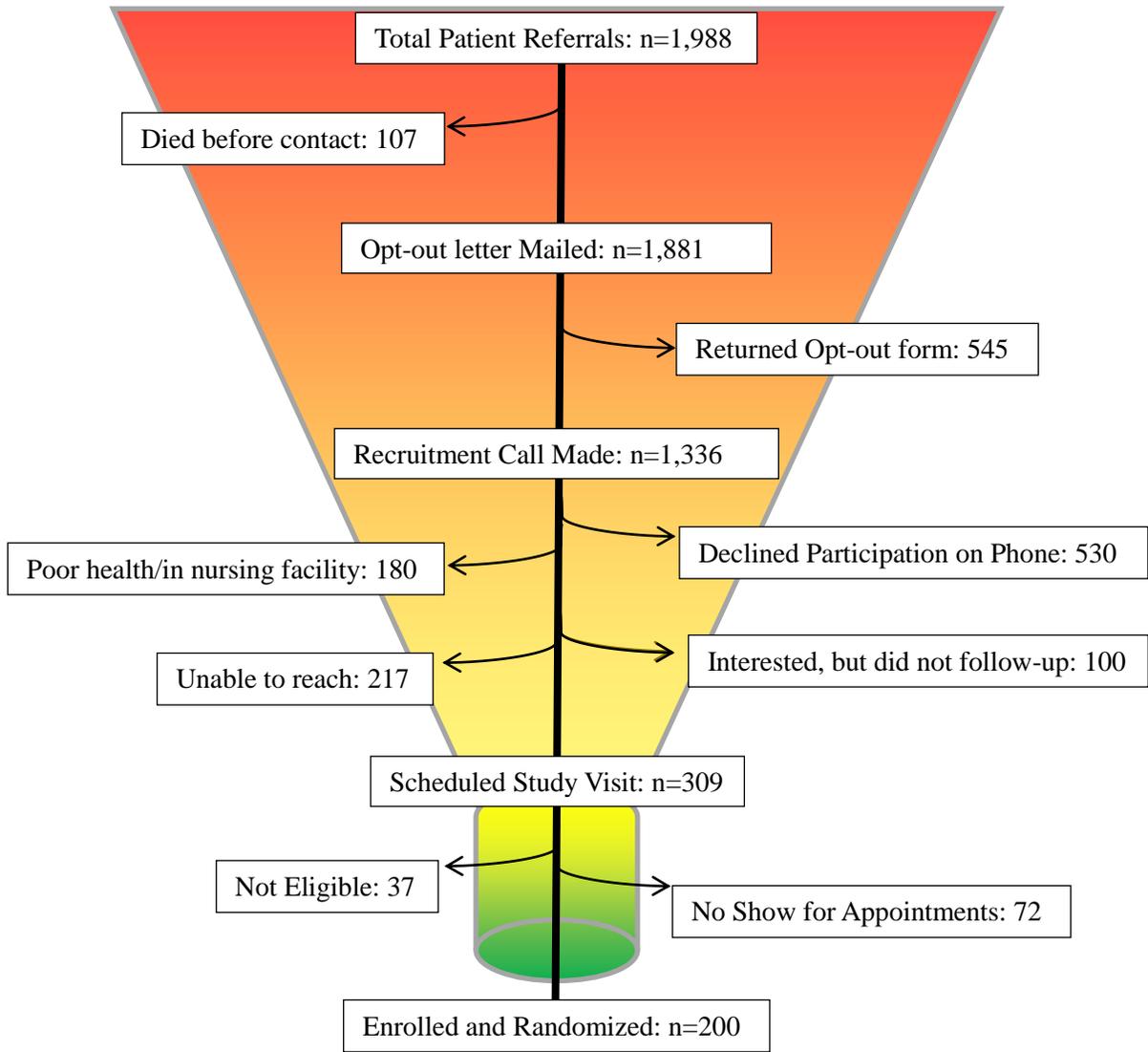


Figure 3: Recruitment Flow

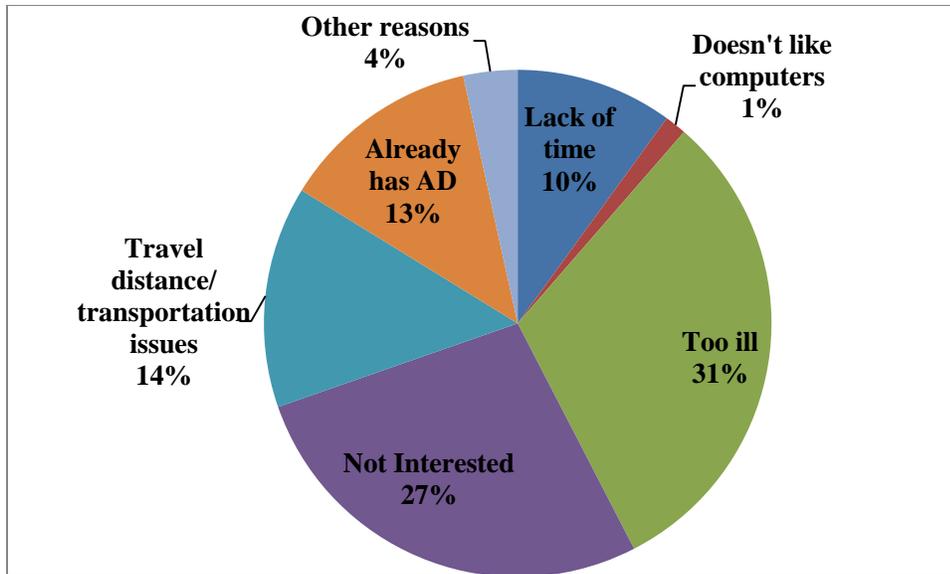


Figure 4: Reason for Declining, n=290

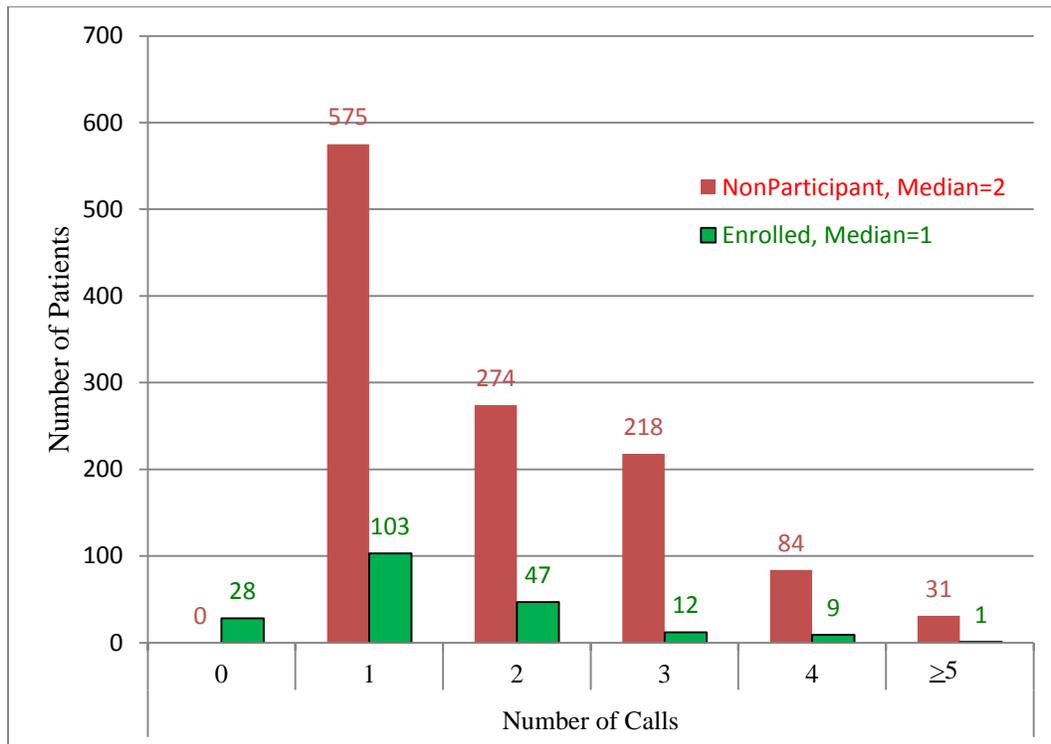


Figure 5: Number of Follow-Up Phone Calls: chi-square test $p < 0.001$

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