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ORIGINAL RESEARCH

Minority Veterans Are More Willing to Participate in Complex Studies Compared to Non-minorities

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Abstract
Background Minorities are an underrepresented population in clinical trials. A potential explanation for this underrepresentation could be lack of willingness to participate. The aim of our study was to evaluate willingness to participate in different hypothetical clinical research scenarios and to evaluate the role that predictors (e.g. health literacy) could have on the willingness of minorities to participate in clinical research studies.
Methods We conducted a mixed-methods study at the Miami VA Healthcare system and included primary care patients with hypertension. We measured willingness to participate as a survey of four clinical research scenarios that evaluated common study designs encountered in clinical research and that differed in degree of complexity. Our qualitative portion included comments about the scenarios.
Results We included 123 patients with hypertension in our study. Of the entire sample, ninety-three patients were minorities. Seventy per cent of the minorities were willing to participate, compared to 60 per cent of the non-minorities. The odds ratio (OR) of willingness to participate in simple studies was 0.58; 95 per cent CI 0.18–1.88 p=0.37 and the OR of willingness to participate in complex studies was 5.8; 95 per cent CI 1.10–1.31 p=0.03. In complex studies, minorities with low health literacy cited obtaining benefits (47 per cent) as the most common reason to be willing to participate. Minorities who were not willing to participate, cited fear of unintended outcomes as the main reason.
Conclusions Minorities were more likely to be willing to participate in complex studies compared to non-minorities. Low health literacy and therapeutic misconception are important mediators when considering willingness to participate in clinical research.

Keywords Minorities · Clinical trials · Health literacy · Participation

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Introduction

Appropriate representation of ethnic minorities in studies is not only essential to produce valid and generalizable results (Britton et al. 1999) but most importantly also represents one of the three principles of the Belmont report, the principle of justice (Allmark 2004). The principle of justice not only ensures equal opportunity of study participation amongst individuals but also that benefit and harm are equally distributed amongst them.

Minorities are underrepresented in cancer clinical trials, (Byrne et al. 2014) and two important factors

could be related to this phenomenon. The first is lack of access to care, and the second is the belief that racial and ethnic minorities are less willing to participate in health research (Murthy, Krumholz, and Gross 2004). The foundation of this latter belief stems from distrust of public health institutions due to past abuses, particularly within the African-American community (Hussain-Gambles, Atkin, and Leese 2004). A pooled secondary analysis of the enrolment decisions of several non-intervention and intervention studies showed that minorities were as willing as non-Hispanic whites (NHW) to participate in health research (Wendler and Grady 2008; Wendler et al. 2006). However, since willingness and the reasons for willingness to participate were not measured at the time of recruitment but rather with informed consent rates, the authors could not evaluate the impact that other factors could have on willingness to participate.

The primary aim of this study was to evaluate the willingness to participate in different hypothetical clinical research scenarios and to evaluate the role of predictors such as health literacy, race/ethnicity, or burden of disease in minorities' willingness to participate. A secondary aim was to evaluate therapeutic misconception (TM) amongst those who were willing to participate in clinical trials.

Methods

Study Design and Setting

The study was a mixed-methods design conducted at the Bruce Carter Miami Veterans Affairs Medical Center between January 2013 and December 2014. We approached patients from each of the medical centre's four primary care clinics before their scheduled visit. The Miami VA institutional review board approved the study.

Study Subjects

We included English-speaking veterans, greater than thirty years of age, who had a diagnosis of hypertension. Hypertension was defined to be a patient who had an ICD-9 code of 401, 405, or 437.2. (Tamariz et al. 2015). The positive predictive value of hypertension codes is 93 per cent. The rationale for using hypertension was that it is a highly prevalent diagnosis, and we could also tailor the willingness to participate scenarios to hypertension to increase potential study enrolment. We excluded patients with a diagnosis of depression or cognitive impairment in their problem list and/or those who were being prescribed medications for depression. The rationale for this exclusion was to minimize the effect these two conditions could have on cognitive function. Depression has been linked to increased likelihood of refusal to participate in clinical research, (Cohen et al. 2004) and cognitive impairment could lead to a lack of comprehension of the materials and informed consent.

Definition of Minority

We collected race and ethnicity information using the census definition of race and ethnicity. We defined an individual to be a minority if the patient self-reported being Black or Hispanic. We included other ethnicities such as Asian/Pacific Islanders and Native Americans but there were no such participants in the study. Non-Hispanic whites were considered the control group. Due to the small sample size, we combined both Black and Hispanic into a single category of minorities.

Definition of Willingness to Participate in Clinical Research

We used a survey to evaluate willingness to participate in clinical research. The survey was developed by L.T. and E.N.M. The survey consisted of four clinical research scenarios of increasing complexity that evaluated common study designs encountered in clinical research. The first scenario was an uncompensated cross-sectional study that gathered information through a survey and medical record abstraction. The second scenario was a minimally compensated cross-sectional study that gathered information through survey, medical record abstraction, and blood draw. Scenario one and two did not share information. The third scenario was a compensated cohort study with a one-year follow-up and gathered information through survey, medical record abstraction, and blood draw. In this scenario, there was also no sharing of information with outside entities. The fourth scenario was a compensated randomized clinical trial of a new blood pressure medication with a five-year follow-up and gathered information through survey, medical record abstraction, and blood draw. However, in this scenario, information was shared with outside entities. To minimize the effect that compensation could

have on willingness to participate, the same compensation was given for scenarios two through four. The survey used a five-point Likert scale, which ranged from "not willing to participate" to "completely willing." We defined willingness to participate to be those patients who selected either "very willing" or "completely willing" on the survey.

We labeled scenario one a simple study and scenario four as a complex study.

Covariates

We collected demographic information that included self-reported age, marital status, gender, education, and income. We measured education as the highest level of formal education completed. Income was defined as the income of all members in the household for the given year and was stratified as low-income if they earned less than 30,000 U.S. dollars a year (Mounsey et al. 2017). We measured health literacy using the Newest Vital Sign (NVS), which is a reliable and valid instrument of measuring health literacy. The NVS consists of a nutritional label that is accompanied by six related questions. Veterans with more than four correct responses are unlikely to have low health literacy, whereas those with fewer than four correct answers indicate the possibility of limited health literacy (Weiss et al. 2005).

We measured years with hypertension to be the number of years since the first reported diagnosis of hypertension. After obtaining informed consent and HIPAA authorization, we collected information from the research subject's medical record. We obtained the blood pressure reading from the electronic medical record on the day the patient was seen in clinic.

Qualitative Analysis

Each scenario had a comments section to elicit reasons why subjects would be willing or unwilling to participate. We stratified the comments by minority group and health literacy status. Each comment was classified into specific domains previously identified in a systematic review of barriers and facilitators for minority research participation (George, Duran, and Norris 2014). These domains included: trust, mistrust, fear of unintended consequences, competing demands and time constraints, lack of access, perceived benefits, and altruism.

Therapeutic misconception (TM) was also evaluated by minority group and health literacy status for those who were willing to participate in scenario four. We defined TM as the lack of differentiation between clinical care and research; therefore, attributing a clinical trial as intent to alleviate or cure a disease. We considered three domains of TM that included: incorrect expectation of individualized care, incorrect assessment of risks and benefits, and incorrect understanding of the goal of the study (Lidz et al. 2015).

Each comment was evaluated by two authors and disagreements were resolved by consensus.

Statistical Analyses

We compared baseline characteristics, at the time of the survey, by minority status using Pearson's chi-square statistic for categorical variables and t-test for continuous measures. Some continuous variables were not normally distributed, and therefore we used the Wilcoxon rank-sum test.

To evaluate univariate differences, we reported the percentage of subjects who were willing to participate by minority status using the chi-square test. To determine predictors of willingness to participate in clinical research, we used logistic regression to calculate the odds ratio (OR) of being willing to participate and the corresponding 95 per cent confidence interval (CI). The model included age, health literacy (continuous variable indicating higher literacy), educational level (categorical variable indicating less than high school), income (continuous variable indicating higher income), and years with hypertension. Analyses were performed using STATA (College Station), and all significance tests were two-tailed.

Results

Baseline Characteristics

We included 123 patients with hypertension in the study. Table 1 shows the baseline characteristics of the entire cohort by minority status. Minorities represented the majority of the cohort (76 per cent). As a whole, minorities were significantly younger than whites ($p<0.01$). However, education, income, marital status, health literacy, and blood pressure were similarly distributed between minorities and whites ($p>0.05$).

Table 1 Baseline characteristics by minority status

Characteristic	Non-minorities (N=30)	Minorities (N=93)	p-value
Mean age (standard deviation)	66.9+/-10.3	60.1+/-8.0	<0.01
Hispanic	NA	39%	NA
High school education or less	37%	31%	0.57
Income <$30.000 or less	20%	12%	0.68
Married	50%	58%	0.46
Mean health literacy (standard deviation)	2.96+/-3.64	2.80+/-2.0	0.71
Number of years with hypertension (standard deviation)	7.03+/-3.64	6.94+/-4.24	0.91
Mean systolic blood pressure (standard deviation)	135.6+/-16.0	134.4+/-17.0	0.73

Comparison of baseline characteristics between minorities and non-minorities. The table shows that minorities and non-minorities had similar characteristics, except for age. It also shows that the majority of the minority group was Black.

Willingness to Participate by Minority Status in Any Study

Minorities (70 per cent) were more willing to participate in any clinical research study when compared to non-minorities (60 per cent); however, this difference was not statistically significant (p=0.31). Willingness to participate also decreased as the complexity of the study increased (p<0.01).

Willingness to Participate by Minority Status and Complexity of Studies

Figure 1 reports the univariate willingness to participate by minority status and complexity of the study. In simple studies, 53 per cent of minorities were willing to participate, compared to 50 per cent of non-minorities. Similarly, in complex studies, 28 per cent of minorities were willing to participate compared to 7 per cent of non-minorities.

Predictors of Willingness to Participate in Clinical Research

The OR of willingness to participate for minorities in simple studies was 0.58; 95 per cent CI 0.18–1.88 p=0.37 and the OR of willingness to participate in complex studies was 5.8; 95 per cent C.I 1.10–1.31 p=0.03.

Table 2 reports the predictors of willingness to participate in simple and complex studies. A higher health literacy (OR 1.33) and higher systolic blood pressure were associated with willingness to participate in simple studies, as was a higher educational level (OR 0.21). In complex studies, none of the other predictors were related to willingness to participate.

Qualitative Barriers, Facilitators and Therapeutic Misconception

We identified participant comments in ninety surveys (73 per cent response rate). In simple studies, minorities cited altruism (60 per cent) as the most common reason to be willing to participate, while competing demands (88 per cent) was the most common reason to not be willing to participate. In complex studies, minorities cited obtaining personal benefits (47 per cent) as the most common reason to be willing to participate. Minorities, who were not willing to participate, cited fear of unintended outcomes as their most common reason. For complex studies, minorities were more likely to cite TM (22 per cent) compared to non-minorities (5 per cent).

Subsequently, in simple studies, a similar pattern was seen for low health literacy participants who were willing to participate. For complex studies, amongst those with low health literacy, the possibility of obtaining benefit (50 per cent) was cited as a common reason to be willing to participate; meanwhile, amongst those with normal health literacy, obtaining benefit was only cited in 25 per cent of the comments. Fear of unintended outcomes was cited as the most common reason to not be willing to participate for complex studies in both low and normal health literacy participants.

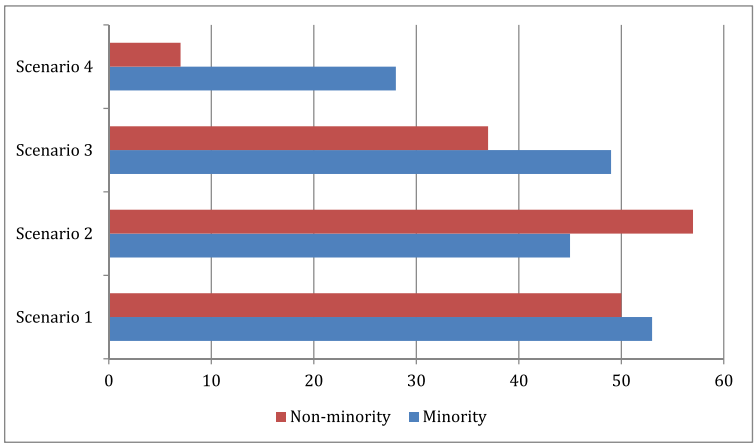

Fig. 1 Willingness to participate by clinical research scenario and minority status

Discussion

Our study found that minorities reported a higher willingness to participate in complex clinical trials when compared to non-minorities. We found that a higher level of education and health literacy only predicted willingness to participate in simple studies, not in complex studies. There are several strengths of this study. First, we evaluated the willingness to participate in clinical trials amongst a population with hypertension, a disease that is not immediately life threatening. Currently, most of the data regarding willingness to participate refers to cancer trials. Secondly, we evaluated predictors that have not previously been examined to determine their effect on willingness to participate in clinical research. Additionally, a mixed-methods approach was used, which gave insight regarding the reasons of willingness to participate.

Our study can be weighed with several limitations. First, our sample size is small, particularly for NHW, limiting our comparison within minority groups. Second, we used a hypothetical example instead of a real study where consent rates can be evaluated. Third, by participating in a study to evaluate willingness to participate, these participants might be inherently different than subjects who did not agree to participate. Fourth, the generalizability of our study is limited to veterans with hypertension. Fifth, our scenarios were intentionally made different in order to assess the effect of increasing scenario complexity on willingness to participate; however, we were unable to evaluate which specific factor was most influential..

There is considerable debate on whether racial and ethnic minority groups, especially African Americans, are less willing than NHW to participate in clinical research. There are many factors that support this notion as demonstrated by cancer clinical trials. However, this notion has been disproved by two large studies. The first, Wendler et al. (2006), reported a pooled secondary analysis of the enrollment decisions of several non-

Table 2 Predictors of willingness to participate in clinical research

Predictors	Simple study		Complex study	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Minority	0.58 (0.18-1.88)	0.37	5.8 (1.10-31.0)	0.03
Health literacy	1.33 (1.06-1.67)	0.01	1.00 (0.73-1.35)	0.98
Education	0.21 (0.07-0.63)	<0.01	2.52 (0.73-8.6)	0.14
Income	1.01 (0.38-2.69)	0.97	0.66 (0.22-2.00)	0.46
Years with hypertension	1.08 (0.95-1.22)	0.19	0.98 (0.86-1.13)	0.86
Age	0.96 (0.89-1.03)	0.28	0.99 (0.91-1.07)	0.92
Systolic blood pressure	0.96 (0.93-0.99)	0.03	0.99 (0.95-1.03)	0.74

intervention and intervention studies which showed that minorities were comparatively as willing as NHW to participate in health research. A second study by Katz et al. (2007) used a population-based survey to measure the likelihood of participation in clinical research and found that all ethnicities reported a similar likelihood of participation.

Minorities are underrepresented in clinical trials. However, this underrepresentation may not be a function of willingness to participate but rather that minorities are not being asked to participate. Efforts have to be channeled into ensuring that minority populations have access to clinical research. Our study found that minorities are indeed more willing to participate in complex clinical trials. Potential explanations for this finding could be altruism (Zuniga et al. 2007), perceived benefits of participation such as monetary compensation, access to medical services, or therapeutic misconception (Lavori, Wilt, and Sugarman 2007).

Therapeutic misconception is the lack of differentiation between clinical care and research; therefore, attributing a clinical trial as intent to alleviate or cure a disease (Appelbaum and Lidz 2008). There are three dimensions of TM : incorrect expectation of individualized care, incorrect assessment of risks and benefits, and incorrect understanding of the goal of the study (Thong et al. 2016). Our study found that minorities and low health literacy participants had a higher TM in clinical trials—particularly the expectation of individualized care and incorrect assessment of risks. Therapeutic misconception is a prevalent finding, ranging from 60–75 per cent of participants in clinical trials (Lidz et al. 2015), chronic disease trials, as well as psychiatric studies (Thong et al. 2016). Risk factors associated with TM are: older age, low educational level, cognitive deficits, and lack of independence (Thong et al. 2016).

Low health literacy is prevalent throughout veteran populations (Rodriguez et al. 2013), particularly in minority groups. It is related to adverse health care outcomes, and in clinical research it is related to a lack of informed consent comprehension (Tamariz et al. 2013). Our study found that in simple studies, higher health literacy was associated with willingness to participate, but the same association was not found for complex studies. The differential effect of literacy and education by complexity of the study is a thought-provoking finding. It indicates that potential research participants understand the possible risks and benefits of simple studies, but having a higher educational level does not have an influence on understanding these risks and benefits. The higher prevalence of TM and the preferential willingness to participate in research according to health literacy status suggests a role in decision-making.

Unfortunately, physicians perpetuate TM. Surveys of oncologists have found that at least 50 per cent believed their patients would be getting "state of the art" treatment by enroling in a clinical trial (Joffe et al. 2001). Another potential perpetuation of physician TM is the researcher enrolment of patients. Patients see clinicians as physicians rather than researchers; therefore, when clinicians enrol research participants, particularly when they enrol their own patients, they can see their participation in research as part of their clinical care and can lead to TM (Brody and Miller 2003).

The confluence of patient and physician TM in low health literacy minorities willing to participate in clinical trials creates a challenge for all research stakeholders that needs to be addressed.

The ethical implications of this study are both theoretical and practical. The theoretical implication of the study is that we have linked low health literacy minorities with participation in complex trials and therapeutic misconception as a potential cause for this differential participation. The practical implications are that health centers with large minority populations and a high prevalence of low health literacy patients, have a moral obligation to ensure adequate comprehension of the informed consent and to minimize TM as a reason for participation.

We currently have an underrepresentation of minorities in research, despite efforts from the NIH and Institute of Medicine. In this context, learning that minorities are willing to participate in clinical trials, specifically complex trials, can prove to be beneficial. Dissemination approaches that mass identify minorities eligible for recruitment, such as those using electronic medical records, claims, or geocoding, could capitalize on minorities' willingness to participate (Tamariz et al. 2015; Palacio et al. 2011). Nevertheless, we also found that minorities who reported that they were willing to participate in complex studies have lower health literacy and were more likely to have therapeutic misconception. This poses an important ethical challenge that needs to be addressed decisively. We hope to improve minority representation but not at the expense of including research subjects who do not fully understand the implications of their participation. The resolution of this challenge is key to ensure fair minority representation.

The ethics community has an important role to play in finding and disseminating solutions. Amongst them, disseminating strategies to ensure informed consent comprehension is a priority. Moreover, leading a discussion about how ethics committees and sponsors should monitor informed consent comprehension is timely and necessary. Such strategies could increase the burden on investigators and administrative efforts and therefore could bring about institutional resistance. However, the prospect of including research subjects who do not understand the risks of participation should justify this discussion.

In conclusion, minorities are more likely than non-minorities to report willingness to participate in complex clinical trials that involve risks. Health literacy plays a role in the decision-making process of subjects participating in clinical research. Therapeutic misconception is an unfortunate prevalent finding in minorities who are willing to participate. Future studies should evaluate interventions to address low health literacy and therapeutic misconception in improving comprehension of informed consents measured by objective means.

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