

# How Informed Is Informed Consent?

## The BHAT Experience

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**ABSTRACT:** In the Beta-blocker Heart Attack Trial (BHAT) a number of strategies were implemented to increase the probability of informed voluntary consent among survivors of an acute myocardial infarction. To evaluate the subjects' comprehension of the study, a bioethicist conducted in-depth home interviews with a random sample of 64 participants from 11 geographic areas. The great majority of respondents proved to be well informed about the study design, its scientific logic, and possible risks of the experimental drug. However, five subjects (8% of the sample) appeared to believe they were involved in a therapeutic program rather than a research project. The analysis of predictor variables indicates that education, race, and age were associated with the degree of respondent awareness of fundamental aspects of the trial.

**KEY WORDS:** *informed consent, interviews, demographic variables.*

### INTRODUCTION

The Beta-blocker Heart Attack Trial<sup>1</sup> is a double-blind placebo-controlled trial of propranolol among approximately 4000 survivors of an acute myocardial infarction [1]. Subjects 30 through 69 years of age were recruited during hospitalization for the acute event and are to be followed from 2 to 4 years. They were randomly assigned either active treatment or placebo therapy (on a 50/50 basis) and remain on that regimen over the course of the study. The purpose of the trial is to test whether the regular use of propranolol can prolong the lives of heart attack patients. This article evaluates subject awareness of the basic features of BHAT.

Because informed consent to enter BHAT had to be obtained so soon after the patient's qualifying infarction, administrators of the study were concerned that eligible candidates might have special difficulties understanding the de-

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sign of the trial and resisting pressure to participate [2]. It was, therefore, decided to incorporate a number of safeguards into the consent process. To facilitate this effort a bioethicist (the senior author) was added to the project staff for BHAT. In cooperation with the administrators of the study and its principal investigators, she implemented the following strategies to increase the probability of truly informed voluntary consent:

1. A model consent form was developed and recommended to the 32 participating centers for their consideration. It contained facts pertinent to each of the six basic categories of information in the DHEW guidelines for informed consent [3]: risks, benefits, procedures, therapeutic alternatives, the option of withdrawal, and the right to ask questions.<sup>2</sup> Many of the centers adopted the model intact. The others used it as a guide.
2. Every consent form proposed or adopted by the participating centers was reviewed by the bioethicist. Where basic information was missing, the facility was urged to improve its form in that regard.
3. A detailed patient information brochure was printed for distribution to prospective subjects [5]. It described important aspects of the research design, eligibility criteria, benefits and risks of participation, and monitoring procedures. None of the centers was required to distribute the brochure, but the project office encouraged its use.
4. Guidelines for obtaining informed consent in BHAT were published and made part of the protocol for the trial [6]. They described for the assembly of investigators what the project office considered to be essential information for eligible patients. In addition, as a more novel approach, they set forth ten procedural safeguards to assure careful deliberation and voluntary consent. These safeguards included the involvement of family members in the explanatory process, constraints on hasty decision making, and constraints on subtle coercion.

To evaluate the adequacy of the informed consent process, the bioethicist conducted in-depth home interviews with a random sample of subjects. They were selected from a random third (eleven) of the 32 participating centers, and the interviews took place 2 weeks to 15 months after the respondents had joined the trial. It was, therefore, possible to measure the patients' understanding of BHAT over time.

## METHODS

It was initially decided to interview five patients from each of the 11 clinics (55 subjects in all). However, the sample actually consisted of 65 patients because ten of those selected were unavailable for home interviews when the bioethicist first appeared in their geographic area. Each was replaced with a randomly chosen substitute, and later everyone who was missed was also

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<sup>2</sup>After BHAT began two more categories of information were added. Prospective subjects must now be advised whether medical treatment or compensation is available if they are injured in the study and whether confidentiality of identifying records will be maintained [4].

**Table 1** Demographic Characteristics of the Respondents at Recruitment

	N	%
<b>Gender</b>		
Male	56	87.5
Female	8	12.5
<b>Age</b>		
30-39	7	10.9
40-49	15	23.4
50-59	25	39.1
60-69	17	26.6
<b>Education</b> (highest attainment)		
<7 years	1	1.6
7-9 years	9	14.1
10-11 years	9	14.1
H.S. diploma	17	26.6
Some college	13	20.3
College degree	8	12.5
Advanced degree	7	10.9
<b>Race</b>		
White	56	87.5
Oriental	1	1.6
Black	7	10.9
<b>Marital status</b>		
Married	54*	84.4
Not Married	10	15.6

\*The physician-daughter of the subject who did not speak English was married, but the subject was not.

interviewed, in person (two) or by telephone (eight).<sup>3</sup> One subject who had withdrawn from the study declined to be interviewed, reducing the response rate to 98%. The demographic characteristics of the 64 respondents are presented in Table 1.

To avoid a biased emphasis on informed consent, none of the centers was told it was among the select group until two weeks before interviews were to be conducted in that area. The clinic coordinator then approached each person in the sample to ask permission for the bioethicist to contact the subject directly.<sup>4</sup>

Whenever possible, the patient and his or her spouse were interviewed together. This procedure was used to learn about the consent process and the cognitive steps preceding the patient's enrollment in the trial. Fifty-three of the 64 subjects were married, and 42 of the spouses were interviewed.<sup>5</sup> In

<sup>3</sup>No constraints were placed on the sampling process for a given clinic. Two weeks before the scheduled visit the sample was chosen, and everyone who had been recruited (including those who were no longer under active follow-up) had an equal chance to be selected. Moreover, none of the selectees had to be replaced because of death.

<sup>4</sup>The patient was told by the coordinator and bioethicist that the sponsors of BHAT (the "Heart Institute in Washington, D.C.") wanted to have closer contact with participants in the study. Therefore, five patients from that clinic were selected by lottery to be interviewed in person by Dr. Howard. The interview would focus on patients' views of the study and how they were "getting along" in taking their medications. Everyone had the opportunity to decline the interview, but only one patient did so.

<sup>5</sup>No attempt was made to interview spouses of patients who were contacted by telephone, which accounts for six of the missing interviews with spouses.

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three instances a daughter also participated in the discussion, and on one occasion a patient's mother was present.

Comments of spouses can be distinguished from those of subjects, but it is impossible to know what each person would have said in the other's absence. Therefore, the concept of "awareness" in the discussion to follow refers to the family's understanding of BHAT, not simply to the participant's views. Since a number of wives and husbands seemed better informed about certain aspects of the trial than the subjects themselves, the inclusion of spouses in the interview process probably increased the comprehension scores of family units.

Almost all the questions were open-ended, and no hints were given as to appropriate answers. Contrary to true-false or multiple-choice testing [7,8], the respondents were required to state their perceptions in their own words. Their comments were then coded to indicate their degree of understanding of selected aspects of the trial. These dimensions of awareness were treated as discrete variables and as components of an overall score. Lastly, certain characteristics of the respondents were tested as possible predictors of awareness.

## LEVELS OF UNDERSTANDING

In evaluating the adequacy of informed consent in BHAT, the most important question is whether the respondents knew they were involved in research as opposed to pure therapy. At a minimum, subjects should have been cognizant of the fact that the medication prescribed in BHAT was being tested to determine its efficacy, i.e., that participants were involved in some kind of experiment [9]. Fifty-eight of the 64 respondents were clearly aware of BHAT's research focus, and the physician-daughter of an additional subject, who spoke no English, fully comprehended the study's purpose.<sup>6</sup> The other five participants and their families (8% of the sample) gave no meaningful indication that BHAT was a research project. They appeared to believe they were involved in a special therapeutic program for rehabilitating heart attack victims.

### Awareness of the Control Group

With two exceptions every respondent who did understand that BHAT was a research project also knew that a control group was included in the design. Thus, 57 subjects (89% of the sample) recognized that some participants took the experimental drug while others took a different substance. Fifty-three of these subjects were additionally aware that the control substance was simply a placebo or "sugar pill." The other four respondents could not identify the control therapy, but one felt it might be the standard medication for the problem of interest.

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<sup>6</sup>Throughout the discussion to follow, that particular daughter is considered the respondent for that family unit.

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To assess the depth of the subjects' understanding of the experimental design, every person who mentioned the placebo or control therapy was asked why such medication was included in the study. The printed brochure for subjects stated that the placebo, double-blind approach "reduces the possibility of drawing false conclusions about how the drug itself is affecting patients" [5], and the guidelines for obtaining informed consent encouraged the investigators to discuss this point [6].

As a result of the information provided and their prior sophistication, 52 of the 57 respondents who were aware of the control group gave at least one cogent reason for its existence. The most common reasons cited were (1) to compare the effects of the real drug and the control therapy under equivalent conditions, (2) to take account of psychological factors that could influence the study, and (3) to make the study valid and objective.

### Awareness of Purpose

The primary purpose of BHAT is to test the effect of propranolol on the survival of patients who suffered an acute heart attack immediately prior to entering the trial. In the patient information brochure, survival and death were deemphasized and the stated purpose of the trial was "to test whether propranolol will reduce the risk of recurrent heart attacks" [5].

All the subjects who were interviewed were asked to summarize BHAT's purpose in their own terms. Their comments were considered correct under either of two conditions: If they mentioned that the medication was being tested to see whether it prolonged the lives of heart attack patients *or* if they mentioned that the drug was being tested to see whether it reduced recurrent heart attacks. Comments suggesting that the purpose of the program was to prevent future heart attacks were considered incorrect unless there was also recognition of the concept of research.

Forty-three respondents gave a completely accurate description of the purpose of the trial, and another eight simply neglected to include the notion of secondary prevention (testing the reduction of "recurrent" attacks). Thus, 80% of the subjects were impressively cognizant of BHAT's purpose. Almost all of them focused on reduced heart attacks rather than prolonged survival. Eight of the remaining subjects recognized that the medication was being tested to see whether it would be helpful, but they did not specify (even with probes) what they meant by "helpful." The other respondents focused entirely on the monitoring and treatment aspects of the program, or they declined to venture an opinion.

### Awareness of Side Effects

Some subjects were already familiar with propranolol before they entered the trial. Others became aware of possible side effects through the patient information brochure, the consent form, discussions with health professionals and friends, and commentaries in the press. A few patients or their spouses consulted the Physicians Desk Reference or similar books on drugs. Further-

more, by the time they were interviewed a number of respondents had had first-hand experience with side effects or inferred their signs and symptoms from physician inquiries at study visits.

When the interviewer asked whether the medication prescribed in the study had any potential for causing side effects, 55 respondents (86% of the sample) expressed awareness of this possibility. However, only 39 subjects or their families (61%) could identify a specific effect. Thirty-eight of them mentioned annoying problems such as fatigue, nausea, and vivid dreams, while 23 identified more serious reactions such as congestive failure and shortness of breath. Thus, 22 respondents were specifically cognizant of both types of problems—the milder effects and the severe.

In most of the consent forms and a follow-up brochure [10], participants in BHAT were also informed about the withdrawal effects that can occur if the use of propranolol is abruptly terminated. Each respondent was, therefore, asked if anything had been said about stopping or not stopping the study medication on the patient's own initiative. Forty-five persons (70% of the sample) correctly replied that no one should abruptly stop taking their tablets without first contacting the BHAT staff.

Another 11 respondents misinterpreted the question and assumed the interviewer was trying to assess their commitment to the trial [11] or their knowledge of their right to terminate participation at any time. Upon further probing, however, several persons in this group indicated incorrectly that a patient could safely stop the drug whenever he wished. The remaining eight respondents in the sample also appeared to be unaware of the drug's withdrawal effects.

### Awareness of the Assignment Process

Each of the 57 subjects who knew of the control group was asked how it was decided to give some patients the experimental medication and others the control therapy. Only 27 respondents (47% of the subsample) expressed awareness that the assignments were based on chance. Another five patients said the selections were made by someone geographically distant (in Washington or Texas, where the coordinating center is located), but they failed to mention the concept of randomization. The remaining 25 subjects had no idea how the assignments were made, or their guesses were totally incorrect.<sup>7</sup>

Among those aware of the control group, 32 respondents (56%) also understood that the distribution of participants to the experimental and control therapies was 50/50. The other 25 subjects did not know what proportion of patients were allocated to each category. Many persons who understood that the assignments were random were unaware of the 50/50 distribution, and vice versa. Only 18 respondents grasped both ideas.

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<sup>7</sup>It did not seem appropriate to ask the respondents who were unaware of the control group about the assignment process; but consistent with their therapeutic orientation, two of them presumed their prescriptions were based on clinical information.

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### Awareness of the Double Blind

Everyone who was cognizant of the control group also recognized that they were not supposed to know whether they were assigned the real medication or the control therapy. When they were asked why the study was designed in this manner, almost everyone gave a relevant response. They noted that the "blind" enhanced compliance to the study, that it gave patients peace of mind, that it made the study more accurate and objective, and that it reduced the influence of suggestibility on symptoms and reactions. A few respondents also said that heart attack patients might become "violent" if they knew they were not prescribed the real medication.

With regard to the *double blind*, 49 of the 57 subjects (86%) clearly understood that the assignments were concealed from physicians as well as patients, and two other respondents had some sense of this feature. Again almost everyone who was aware of the physician blind appreciated its rationale. They indicated that this approach was necessary to insure the validity of the study, to avoid biased interpretations of clinical data, to reduce the possibility of patient "unblindings," and to guarantee the equal treatment of patients. Two respondents speculated that if the assignments were known to physicians, they might prescribe compensatory therapy for placebo patients and thereby contaminate the results of the study.

### Comprehensive Awareness

To measure the patients' overall comprehension of the trial, every respondent was given one point for each basic component of information that was understood. Lesser credit was given for partially correct answers. A score of 12 was the maximum possible value, symbolizing awareness of the following: the research orientation, the control group, the placebo therapy, the purpose of the trial, the patient blind, the physician blind, the randomization process, the 50/50 distribution, milder side effects, serious side effects, withdrawal effects, and the rationale for the control group.<sup>8</sup>

For the sample as a whole the scores ranged from zero to 12, with an average value of 8.8 and a median value of 9.5. For the 57 respondents who were cognizant of the control group, the scores ranged from 5.5 to 12 with an average value of 9.7 and a median value of 10.<sup>9</sup>

### PREDICTORS OF UNDERSTANDING

In prior studies demographic characteristics have been associated with subject comprehension of research programs [8,12-16]. Therefore, five types of demographic information regarding each participant were selected as possible

<sup>7</sup>The seven respondents who failed to understand that a control group was included in the design could only obtain a maximum score of five because their lack of awareness made half the questions inappropriate.

<sup>9</sup>The eight respondents who were interviewed by telephone because of their mobility or illness were all aware of the control group, and their average score was 9.2.

**Table 2** Percentage of Aware Subjects: Classified by Dimensions of Understanding, Demographic Characteristics, and Time Since Recruitment

Predictor variables	No. in category	No. aware of control group	Research focus		Control group %	Purpose %	Awareness of:		
			%	%			Specific side effects %	Randomization %	50/50 distribution %
Education ≤ High school	36	(29)	86	81	72	56	(41)*	(52)	(79)
College	28	(28)	100	100	89	68	(54)	(61)	(96)
Race									
Blacks	7	(3)	43	43	43	29	—	—	—
Nonblacks	57	(54)	98	95	84	65	—	—	—
Age									
< Median	32	(29)	97	91	78	69	(59)	(62)	(93)
> Median	32	(28)	88	88	81	53	(37)	(50)	(81)
Elapsed Time									
< 4 months	32	(30)	97	94	88	53	(53)	(57)	(90)
> 4 months	32	(27)	88	84	72	69	(41)	(56)	(85)
Total sample	64	(57)	92	89	80 (88)	61 (65)	(47)	(56)	(88)*

\*The parentheses signify that the percentage of aware subjects was based on the subsample who were aware of the control group rather than the total number in the category.

Since only three of the blacks were aware of the control group, these percents were not computed.

The base N here is 56 because one respondent was not asked about the physician blind.

**Table 3** Comprehensive Awareness Scores:  
Classified by Demographic Characteristics  
and Time Since Recruitment

	Number in category	Average overall score <sup>a</sup>
Total Sample	64	8.8
Education		
≤ High school	36	7.9
College	28	10.1 $p < 0.02^b$
Race		
Blacks	7	4.6
Nonblacks	57	9.3 $p = 0.02$
Age		
< Median	32	9.4
> Median	32	8.3 $p < 0.02$
Elapsed Time		
< 4 months	32	9.2
> 4 months	32	8.4

<sup>a</sup>A score of 12 was the maximum possible value for a given subject.

<sup>b</sup>The  $p$  values were determined by a Mann-Whitney U test.

predictor variables. education, race, age, gender, and marital status (Table 1). A sixth factor (length of time from recruitment to the evaluative interview) also seemed a likely correlate of patient understanding [17].

To determine the relationship between the six predictor variables and the respondents' awareness of the trial, seven basic types of understanding were selected as discrete outcome variables (Table 2). In addition, the relationship between each predictor and the comprehensive awareness scores was measured. (Tables 3 and 4). Then to gain a fuller sense of the impact of the predictor variables, a multiple regression analysis was carried out for the most relevant factors, singly and in combination. Neither gender nor marital status had a strong, consistent, or statistically significant effect on respondent awareness; therefore the discussion to follow focuses on the other four variables.

### Education

In the analysis of predictors the educational attainment of the respondents was dichotomized as close to the median as possible, separating those with no education beyond high school from the college group. For all the measures of understanding, the proportion of aware subjects was higher among the better educated (Table 2). However, only one of the differences was statistically significant. Everyone with college training knew that BHAT was a research program involving a control group, compared to 81% of those without any college ( $p < 0.02$ ).<sup>10</sup>

<sup>10</sup>When many statistical tests are performed,  $p$  values should be interpreted cautiously because multiple tests increase the likelihood that at least one difference will reach significance by chance alone. Thus, it is also helpful to consider the magnitude of significance, the degree of internal consistency, comparable data from other studies, and the constraints of sample size on the possibility of significance.

In this paper the term significance is used in a symbolic sense, to refer to  $p$  values  $< 0.05$ . However, conclusions regarding effects of the predictor variables are based on a consideration of the impressively small  $p$  values associated with certain relationships.

**Table 4** Comprehensive Awareness Scores:  
Cross Classified by Education, Race, and Age

Average Overall Scores and Number in Category						
Education	Education		Race		Age	
	≤ High school	College	Blacks	Nonblacks	< Median	> Median
≤ High school			2.4 (5)	8.7 (31)	8.5 (16)	7.4 (20)*
College			10.2 (2)	10.0 (26)	10.3 (16)	9.7 (12)
Race						
Blacks	2.4 (5)*	10.2 (2)			1.0 (1)	5.2 (6)
Nonblacks	8.7 (31)	10.0 (26)			9.7 (31)	9.0 (26)
Age						
< Median	8.5 (16)	10.3 (16)	1.0 (1)	9.7 (31)*		
> Median	7.4 (20)	9.7 (12)	5.2 (6)	9.0 (26)		

\* $p < 0.01$  for the race difference in the rankings of the scores.

\* $p \sim 0.02$  for the age difference in the rankings of the scores.

\* $p < 0.05$  for the education difference in the rankings of the scores.

To measure the overall impact of education, the 64 subjects were ranked in terms of their comprehensive awareness scores, and a Mann-Whitney U test was applied to the data to see if the distributions for the two educational groups were significantly different. The average score for the college group was 10.1 compared to 7.9 for those without college, and the difference in central tendencies had a  $p$  value of  $< 0.02$ .<sup>11</sup> When race was controlled, education continued to be positively associated with awareness, but the  $p$  values fell short of significance ( $p \sim 0.07$  for nonblacks and 0.19 for blacks). Similar patterns were also found when age was held constant, across the sample as a whole and among the nonblacks considered separately. For each age group, those with college training had a higher awareness score than those without college (Table 4).

### Race

Because the total number of blacks was small, the race differences in awareness had large confidence intervals. However, the impressive  $p$  values suggest that the differences were real, not simply the result of chance.

Only three of the seven blacks (43%) recognized they were participating in a research project, while the equivalent figure for the 57 nonblacks was 98% ( $p < 0.001$  by a two-tailed Fisher exact test). Similarly, only three of the seven blacks compared to 95% of the nonblacks ( $p < 0.002$ ) were aware that a control group was included in the study design (i.e., that participants were not necessarily prescribed the experimental drug). When education was held constant, this difference persisted among those with no education beyond high school. Only one of the five blacks was aware of the control group compared to 28 of the 31 nonblacks ( $p = 0.003$ ). Where the subjects had more than a high school education everyone was cognizant of the control group, including the two blacks.

Regarding the purpose of the trial, the proportion of aware blacks was again three out of seven compared to 84% of nonblacks ( $p < 0.05$ ). Knowledge of definitive side effects showed a similar difference which was not significant (Table 2). The average overall awareness score was 4.6 for blacks vs. 9.3 for nonblacks, and the race difference in the rankings had a  $p$  value of 0.02. Among the respondents with no education beyond high school, the race difference was even larger with a  $p$  value of  $< 0.01$ , and the difference was impressive for each grade level in which race comparisons were possible. When age was controlled, the blacks continued to be the less aware group. Moreover, when age and education were both held constant (which was only meaningful for the older patients without college training), the race difference in the rankings of the scores was again statistically significant.

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<sup>11</sup>The Mann-Whitney U test measures whether the sums of the ranks for two distributions of scores are significantly different. Thus, it essentially measures the difference in central tendencies [18].

## Age

The median age of the 64 subjects at the time of recruitment was slightly less than 55 years. For six of the seven discrete measures of understanding, the proportion of aware respondents was higher among the younger group, and in the seventh comparison the proportions were approximately equal. The age effect was greatest for awareness of randomization (Table 2) but none of the differences reached significance. When education was controlled, age had a more consistent and impressive effect on the awareness of those without college training. In that group the proportion of aware subjects was always higher for younger than older patients, and the difference was profound and statistically significant for awareness of randomization. Among the college group the impact of age depended on the measure of understanding, and none of the differences was significant.

Consistent with the analysis of discrete measures of understanding, the evaluation of the comprehensive awareness scores showed higher mean and median values for the younger group of patients. According to the Mann-Whitney test the awareness difference between the two age groups had a  $p$  value of  $< 0.02$ , and the age effect was again more impressive among those with fewer years of schooling (Table 4,  $p \sim 0.07$ ). No age comparisons were possible among the small group of blacks because only one of them was in the younger category. Among the nonblacks, however, the average awareness score was somewhat higher for younger than older patients, and the difference in central tendencies had a  $p$  value of  $\sim 0.02$ .

When education was controlled for the nonblacks, the age effect was similar in both educational groups.

## Time

The median duration of elapsed time from subject recruitment to the evaluative interview was approximately four months. When the respondents were divided into two groups on the basis of elapsed time, there was essentially no confounding of time with the important demographic predictors of patient understanding (education, race, and age). However, the average duration of participation varied considerably from clinic to clinic because all interviews in a given locality were conducted within a 3-day period.

For six of the seven discrete measures of understanding, time had an adverse effect on the subjects' awareness of the study (Table 2), but their recognition of specific side effects appears to have increased over time. None of the relationships was statistically significant, however, and there was no significant difference between the comprehensive awareness scores of patients with shorter and longer elapsed time (Table 3).

## The Multiple Regression Analysis

As a preliminary step in the multiple regression analysis, it was confirmed that only three of the predictor variables (education, race, and age) were meaningfully associated with the respondents' overall awareness of the trial.

Table 5 Multiple Regression p Values for the Predictor Variables\*

	p values
Unadjusted main effects	
Education	0.002
Race	0.0001
Age	0.02
Adjusted main effects	
Education	0.007
Race	0.0002
Age	0.2
Adjusted main effects with one variable constant <sup>b</sup>	
≤ High school	
Race, adjusted for age	0.0002
Age, adjusted for race	0.4
College	
Race, adjusted for age	0.6
Age, adjusted for race	0.04
< Median age	
Race, adjusted for education	0.003 <sup>c</sup>
Education, adjusted for race	0.2
> Median age	
Race, adjusted for education	0.005
Education, adjusted for race	0.005
Nonblacks	
Education, adjusted for age	0.03
Age, adjusted for education	0.09

\*In the relationships described below education was always positively associated with respondent awareness; age was always negatively associated; and except for the subgroup with a college education nonblacks showed greater awareness than blacks.

<sup>b</sup>There were no statistically significant first-order interactions within the subcategories.

<sup>c</sup>In this age category the race comparison involved only one black vs. 31 nonblacks.

Further computations were, therefore, limited to these particular factors.<sup>12</sup> All three main effects in their unadjusted state were highly significant (Table 5), and the effects of race and education were also highly significant when each factor was adjusted for the other two variables simultaneously ( $p = 0.0002$  and  $0.007$ , respectively). However, the effect of age was not significant when adjusted for race and education ( $p = 0.2$ ). Moreover, none of the first- or second-order interactions was significantly associated with the awareness scores, but in samples of this size the power to detect interactions is limited.

In pressing the analysis further, it was, therefore, decided to hold one variable at a time constant in studying interactions and adjusted main effects. Two education groups were held constant (college and noncollege), two age groups (dichotomized at the median), and one racial category (nonblacks). The results of the analysis showed that race and education had highly significant effects on respondent awareness when each factor was adjusted for

<sup>12</sup>Unless otherwise specified, the full range of values were used for education and age, not simply the dichotomies.

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the other two variables and that age had marginally significant effects (Table 5). Consistent with the previous findings, the race difference in awareness, adjusting for age, was highly significant among the noncollege group ( $p = 0.0002$ ) but not among those with greater education ( $p = 0.6$ ).

## DISCUSSION

The great majority of respondents were well informed about the study design and possible risks of participation. Eighty-nine percent knew that BHAT was a research program involving an experimental drug and a control substance. Eighty-six percent realized that propranolol can cause side effects, and 80% correctly described the study's purpose. Among the 57 respondents who were cognizant of the control group, the levels of understanding were even more impressive. Most of the awareness proportions ranged from 88 to 100%.

It is not entirely clear what standard of awareness should be the goal in trials such as BHAT. Is it reasonable to expect 100% of the participants to get perfect scores across the 12 basic types of information discussed above? Should one search instead for a relative standard by inspecting the findings of others?

If one takes that tack, one learns that approximately 40% of pregnant subjects in a randomized trial of labor-inducing therapies were unaware they were participating in research, even though all had signed appropriate consent forms [12], that two-thirds of "wealthy" volunteers in a trial of an anti-inflammatory drug were unaware it could cause peptic ulcers, even though everyone had been told this fact at least three times [7], and that 100% of patients who had consented to open-heart surgery had completely "forgotten" vital information in the consent process when they were asked about it four to six months postoperatively [17]. The literature repeatedly indicates that research subjects and patients undergoing therapeutic procedures do not adequately understand the programs involved [11, 13-15, 19-27]. Should these experiences serve as standards for future investigators to surpass [28]?

In a more optimistic vein, one study showed that healthy laypersons can be taught to understand and remember detailed aspects of a disease such as cholera if they are intensively trained for 1 or 2 days in a research-ward environment [8]. However, 2 days of instruction for BHAT candidates would have been an unethical burden for heart attack patients to bear, and it might also have jeopardized the value of the trial by delaying the initiation of treatment.

Given the acute-care context of recruitment for BHAT and the traditional medical settings in which the follow-up examinations are conducted, it is not surprising that a few respondents thought the program was strictly therapeutic [21, 29]. Even the patients who fully understood the design of the study occasionally indicated by their comments that they, too, believed that BHAT was really a therapeutic program. However, they were able to distinguish between wishful thinking and the reality of research. That reality in BHAT mandated certain behavior patterns that contradict the usual therapeutic relationship between doctor and patient [29]. The medical care process does not normally include randomized therapies, fake medications, concealed prescriptions, and an experimental *modus operandi*.

Only two people in the sample had previously participated in medical research; therefore, generally speaking, they had no equivalent experience to serve as a frame of reference. When they were asked to explain the rationale for the control group and double blind, they were forced to consider and discuss the scientific logic of the research design. This they did well; using examples of studies and tests from their work environments, television commercials, and even horse racing. They did not do as well describing the assignment process or identifying specific risks of participation. Perhaps, the details of allocation no longer seemed relevant, and their awareness of disabling side effects may have been repressed [8,22,24,29].

Since none of the interviews was conducted at the time of consent, selective forgetting may have occurred. Memory has been shown to be influenced by emotion, mood states [30], and pharmacologic agents, all of which could affect the retentive capacity of patients recuperating from a heart attack. However, it seems unlikely that the respondents would have forgotten something as basic as the research orientation of BHAT or the inclusion of a "sugar pill," if they understood those features in the first place. Moreover, their on-going involvement in the study and interactions with the staff should have reinforced their comprehension of certain aspects of the trial such as the double blind.

The analysis of predictor variables indicates that the respondents with less education were less aware of basic features of the trial than the college group, and that among the lesser educated, being black exacerbated the problem. The data also suggest that awareness decreased with age. Similar observations have been made by other investigators [8,12-16]. Further research is necessary to determine the cause of these associations.

On the basis of the literature and comments of the respondents, it would appear that the patients' understanding of BHAT was influenced by their training and experience [29], the clarity and depth of their on-going dialogue with the research staff [12], their independent quest for information about the study [29], their particular reasons for joining the trial [31], and "extraneous" priorities and concerns (such as monetary worries) that can interfere with a patient's concentration and interest in the details of research [7,11-13,25]. These factors may in turn have been influenced by the education level of the respondents and such characteristics as race and age.

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