Informed Consent and Research Subject Understanding of Clinical Trials

Margo Hoover-Regan, MD; Tara Becker, PhD; Mary Jane Williams, MPH, BSN; Yoram Shenker, MD

ABSTRACT

Context: Current evidence suggests many clinical trial participants have incomplete understanding of research objectives and methods.

Objective: Determine consent standards compliance, satisfaction with facility and study staff, and research subject understanding of clinical trials.

Design: Retrospective review of responses gathered when subjects were interviewed at the inception of clinical trial participation.

Setting: Clinical research unit at the University of Wisconsin, Madison.

Patients: Clinical trials participants on the research unit.

Main Outcome Measures: Understanding of the particular trial in which each subject was participating; research team compliance with informed consent standards; and satisfaction with the research facility, staff, and clinical trials teams.

Results: 423 of 570 research participants were oncology patients; 298 were males. Age range was 10 to 90 years old (mean of 56.6 (+/-16.6) years old). Most subjects (99%) had signed the consent form; 97% reported satisfaction with the research facility and 96% with the study staff. Four-fifths of participants had accurate knowledge of study aims, methods, and risks, but 20% of subjects understood considerably less. Oncology subjects were older (mean age 60.1 [+/-12.5] years vs 46.4 [+/-21.9] years, $P < 0.001$). Non-oncology subjects and patients under age 61 demonstrated superior study knowledge ($P < 0.001$).

Conclusion: Compliance with informed consent standards and satisfaction with services and staff was excellent. Future efforts should focus on better informing older subjects and those on oncology trials.

INTRODUCTION

In 2001, the National Institutes of Health (NIH) introduced the requirement of having a Research Subject Advocate (RSA) in every federally funded General Clinical Research Center (GCRC). The primary function of the RSA is to ensure that studies are designed and conducted safely and ethically with protection of human subjects accorded the highest priority. The University of Wisconsin GCRC, a unit of 15 inpatient and 6 outpatient rooms, appointed its first RSA in the fall of 2001. Within the first 6 months, the advocate developed several initiatives aimed at enhancing subject safety and supervising compliance with research regulations and ethical conduct. A quality control initiative was implemented in which a checklist was used to assess individual patient understanding and study staff adherence to informed consent standards. This assessment was done by administering a checklist via a face-to-face interview. This was initially done 3 days per week, and after the addition of a second advocate in September 2006, patients were interviewed on all 5 weekdays. The data were collected from February 2005 through August 2009.

METHODS

Research subjects were interviewed by an advocate, a nurse manager, or both at the inception of participation in a clinical study. On occasion, the same patient was enrolled in a second trial and the data from this separate interview were also included. Typically 1 to 3 patients were seen per day. On less than 10% of the days, there were no new participants to interview. Interviews lasted approximately 5 to 10 minutes.

The checklist contained the following identifying items: room number, participant's initials, age, gender, diagnosis, treatment, and study identification number and title. These items were pre-filled by the nurse manager or charge nurse. Subjects were interviewed individually, and were first asked how they had learned about the study (eg, via their treating physician, a flier,

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Author Affiliations: University of Wisconsin School of Medicine and Public Health Clinical and Translational Research Core, Department of Pediatrics (Hoover-Regan); Department of Biostatistics (Becker); Department of Medicine (Shenker); University of Wisconsin Hospital and Clinics (Williams).

Corresponding Author: Margo Hoover-Regan, 1111 Highland Ave, Rm 4109, Madison, WI 53705-2275; phone 608.263.6200; fax 608.265.9721; e-mail mhooverregan@pediatrics.wisc.edu.

or advertisement). Protocol knowledge then was assessed. The leading question usually was, "What is your understanding of the research study?" followed by more specific questions. In a few cases (estimated at less than 10%), responses provided by a spouse or significant other were accepted in addition to those offered by the subject.

The subject's study knowledge was rated based upon the following 4 criteria: (1) expressed full familiarity with the procedures and medication; (2) included the mechanism of action of the study drug; (3) demonstrated knowledge of research study goals; and (4) had complete knowledge of side effects. Knowledge was rated as excellent if the interviewee answered affirmatively to all 4 data elements; very good if 1 to 2 elements were omitted (most typically this was the mechanism of action of a study drug); fair if 3 elements were omitted; and poor if none of these elements was mentioned.

Subjects were asked if they had been given a signed copy of the consent form and study staff contact information. They also were asked to rate the consent process as appropriate or inappropriate, based on whether or not they felt sufficient information had been provided to allow them to decide if they wanted to participate in the study.

Patient satisfaction with the research unit staff and environment, and the research investigator's team, was rated as high, moderate or low. Additional comments related to these 2 queries, quoted verbatim from the respondents, also were recorded frequently.

Data were analyzed by calculating descriptive statistics for the full sample, by study type (oncology vs nononcology), and gender (male vs female). Differences between groups for categorical variables (eg, study knowledge) were tested using the non-parametric Fisher's exact test. Differences between groups for continuous variables (eg, age) were tested using variance analysis.

The study received an exemption for the need for consent from the University of Wisconsin Health Sciences Institutional Review Board.

RESULTS

Over the period covered in this analysis, 2364 subjects were admitted to the research unit and interviews were conducted with a random sample of 570 research participants (24%). Table 1 shows the descriptive statistics for all patients interviewed. Age ranged from 10 to 90 years.

Table 2 compares oncology study participants to nononcology study participants. The mean age of the oncology study participants was 60.1 (+/- 12.5) years, while the mean age of nononcology study participants was 46.4 (+/- 21.9) years. This difference was statistically significant ($P < 0.001$). Oncology study participants were more likely to be male (57%) compared to nononcology study participants (38%), and this difference was statistically significant ($P < 0.001$).

Table 1. Descriptive Statistics—Full Sample

	N	All Mean/%	SD
Age	**570**	**56.57**	**16.61**
Year of visit			
2005	57	10.3	
2006	154	27.9	
2007	141	25.6	
2008	130	23.6	
2009	69	12.5	
Gender			
Male	298	52.4	
Female	271	47.6	
Type of study			
Oncology	423	74.2	
Nononcology	147	25.8	
Knowledge of study			
Excellent	195	34.6	
Very Good	264	46.9	
Partial	102	18.1	
None	2	0.4	
Consent			
No	5	0.9	
Yes	554	99.1	
Consent process was appropriate			
Appropriate	563	99.8	
Inappropriate	1	0.2	
Satisfaction with CTRC			
High	537	96.9	
Moderate	17	3.1	
Low	0	0.0	
Satisfaction with research staff			
High	533	95.9	
Moderate	22	4.0	
Low	1	0.2	

Abbreviation: CTRC, Clinical and Translational Research Core

Nononcology study participants showed better study knowledge ($P < 0.001$).

Figure 1 shows the probabilities of reporting Excellent, Very Good, or Partial/None study knowledge by age for the oncology participants. Figure 2 shows these probabilities for the nononcology participants. Overall, oncology study participants showed less research study knowledge than non-oncology study participants ($P = 0.001$). The study knowledge was lower among the youngest subjects and then increased until about age 39 before declining among older participants, such that subjects who were older than age 68 had less knowledge about the research study than the youngest subjects.

As shown in Table 3, there were few differences by gender. With respect to age, the 20- to 40-year-old patients were far more likely to be on oncology studies than nononcology studies

Table 2. Descriptive Statistics by Study Type, with Fisher's Exact Test *P*-values

	Oncology			Nononcology			
	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**423**	**60.11**	**12.53**	**147**	**46.37**	**21.93**	**<0.001**
Year of visit							**<0.001**
2005	52	12.8		5	3.5		
2006	123	30.2		31	21.5		
2007	86	21.1		55	38.2		
2008	91	22.4		39	27.1		
2009	55	13.5		14	9.7		
Gender							**<0.001**
Male	242	57.3		56	38.1		
Female	180	42.7		91	61.9		
Knowledge of study							**<0.001**
Excellent	129	31.0		66	44.9		
Very good	196	47.1		68	46.3		
Partial	89	21.4		13	8.8		
None	2	0.5		0	0.0		
Consent							**0.219**
No	5	1.2		0	0.0		
Yes	408	98.8		146	100.0		
Contact information							**0.426**
No	6	1.4		1	0.7		
Yes	413	98.6		144	99.3		
Consent process was appropriate							**0.743**
Appropriate	418	99.8		145	100.0		
Inappropriate	1	0.2		0	0.0		
Satisfaction with CTRC							**0.142**
High	396	96.4		141	98.6		
Moderate	15	3.6		2	1.4		
Low	0	0.0		0	0.0		
Satisfaction with research staff							**0.142**
High	392	94.9		141	98.6		
Moderate	20	4.8		2	1.4		
Low	1	0.2		0	0.0		

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(65% vs 35%), while patients who were ages 41 and over were far more likely to be on nononcology studies (81% of those ages 41 to 60 years and 83% of those over age 60). This difference was statistically significant ($P<0.001$). The relationship between age and study knowledge seen in Figures 1 and 2 can also be seen in Table 4: patients under age 61 are more likely to have excellent or very good study knowledge than patients over age 60 (90% vs 73%). This difference is statistically significant ($P<0.001$). The vast majority of the 217 comments about level of satisfaction with the research unit and study staff were very positive, particularly toward the research unit nurses. Thirty-three comments were negative, most of which were related to delays in starting chemotherapy.

DISCUSSION

The Declaration of Helsinki (1964) and the Belmont Report (1979) established worldwide and national ethical guidelines for human subject research. Ensuring that clinical trials participants are informed of clinical trial goals, benefits, potential risks, methods, and provided the right to choose or refuse participation are key tenets of both documents. However, the declaration fails to define adequate understanding of informed consent. Our report focuses on an institution's efforts to evaluate clinical trials subjects' understanding of these elements, study staff compliance with policies aimed at achieving optimal subject understanding, and subject satisfaction with certain aspects of clinical trial participation.

With the goal of maximizing subjects' comprehension of clinical trials and, in turn, promoting patient/participant autonomy, consent form standards have become quite rigorous and language in the resulting documents is often complex. The content of these complicated forms typically is explained to the potential participant by a member of the research team who is well versed in the methods, risks, benefits, and alternatives to participation in the trial. In theory, this can result in good understanding of the issues at hand and autonomous, truly informed consent, but barriers definitely exist. The potential subject's education level, physical health, and prognosis are but a few factors which might impede comprehension. Furthermore, if the reading level of the form is too high, the subject may not have a realistic chance of understanding the content. Federal regulations are in place to protect patients with diminished cognitive and decision-making capacity; in such situations, the burden of comprehension and weighing risks and benefits may fall on a surrogate or representative.

In an effort to evaluate the effectiveness of the consent process, various methods have been used to assess subjects' understanding of the clinical trials in which they are participating. Specifically, subjects have been interviewed or asked to complete questionnaires. Some investigators have used instruments that rely on self report; that is, participants are asked whether or not they understand aspects of the trial (and sometimes they are also asked to rate the degree of understanding).[1-3] In the majority of studies, however, the investigators themselves determined the level of subjects' comprehension, either by asking open-ended questions in

Figure 1. Predicted Probability for Level of Knowledge about the Study by Age: Oncology

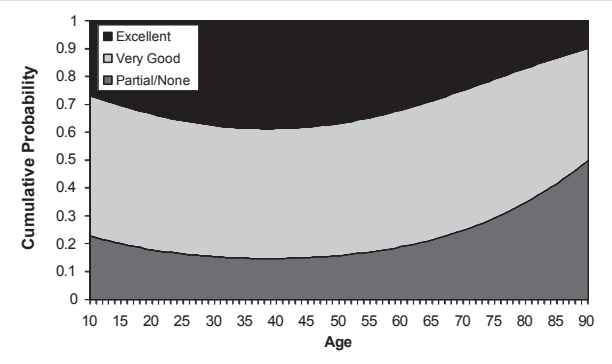
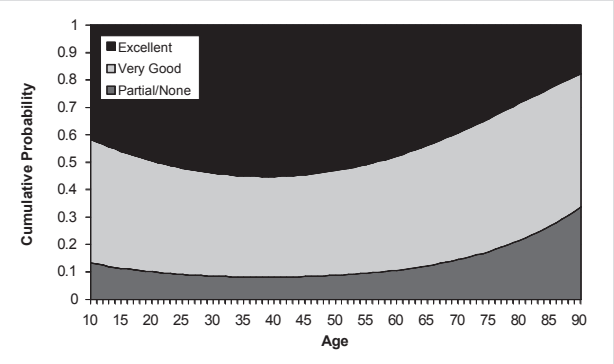


Figure 2. Predicted Probability for Level of Knowledge about the Study by Age: Nononcology



an interview format, focused questions about specific aspects of a clinical trial, or a combination of these 2 types of queries.[4-9] Rarely, these tools have been validated. For example, one study assessed subject understanding of 3 Eastern Cooperative Oncology Group trials via telephone interviews in which participants were asked 23 true/false and multiple-choice questions that had been judged to have high content validity by a panel of experts.[10] While the questions we asked in the current study were not validated, the interviewers thoroughly reviewed each protocol monograph in advance in order to make as accurate a determination as possible of the subject's understanding of the clinical trial.

Despite the existence of policies and rigorous federal guidelines for informed consent in research, subjects' understanding of their clinical trials is often inadequate. This was observed in a 1990 study that evaluated cancer patients' interpretation of a hypothetical cancer therapy trial.[5] Of the 50 patients enrolled, 74% failed to acknowledge that both risks and benefits of trial participation were relevant. Furthermore, of the 30 (n = 50) subjects who agreed to enter the hypothetical trial, 33% focused entirely on the risks of this phase II study. Since then, other investigators have found variable levels of subject understanding. A study assessing brain tumor patients' understanding of a chemotherapy trial found that general trial comprehension was good, patients believed refusal to enroll would not impact treatment and that the decision to participate was voluntary; recall of risks, however, was low.[4] When 156 patients and 37 physicians involved in research projects at 4 Veterans Administration hospitals were interviewed, most patients knew they were research subjects, had voluntarily consented, and knew the details of their treatment, but few understood the research well.[8] Furthermore, readability analysis showed that the consent form language was at a college level of education.

The majority of the subjects in our series were said to have excellent or very good knowledge of the clinical trial in which they participated, but deficiencies were still observed. The specific concepts that proved difficult to grasp were not reported in our series, although other investigators have collected this information. Researchers using a validated measure of consent form quality found that many subjects were unaware of the unproved nature of a treatment, the lack of certainty about trial benefits, and the idea that an important aim was to benefit future patients.[1,4,11] This is an illustration of the therapeutic misconception, which is a failure to distinguish treatment from research evaluating the possible utility of an intervention. In other words, subjects often believe the physician is providing treatment known to be effective when, in fact, he or she is performing an intervention with the intent of learning whether or not it is actually therapeutic. Randomization is also difficult for many participants to understand, which may be a reflection of the therapeutic misconception as patients often feel that their doctor is acting in their best interests by choosing the best therapy for the individual patient. In a survey conducted on rheumatology research participants to determine their satisfaction with the process and ability to understand informed consent, most participants reported they were satisfied with the process and understood the trial concepts. However, the investigator states that trial concepts may be misunderstood regardless of self-assessment of understanding and suggests subjects may prefer to believe investigators know which treatment they are receiving and have made a good treatment decision specific to their case, despite having been told otherwise.[2]

Two aspects of compliance with consent procedures in our series could foster greater understanding of clinical trials methods, risks, and benefits. By having a copy of the signed consent form, subjects would be able to refer back to that document if questions arose. Similarly, by having study staff contact information, subjects would have a means of asking questions and obtaining clarification after the consent discussion had occurred and the form had been signed.

To our knowledge, this is the first report comparing demo-

Table 3. Descriptive Statistics by Gender, with Fisher's Exact Test *P*-values

	Male			Female			
	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**298**	**57.81**	**16.87**	**271**	**55.17**	**16.27**	**0.025**
Year of visit							**0.225**
2005	32	11.3		25	9.1		
2006	86	30.4		68	24.6		
2007	63	22.3		87	31.5		
2008	63	22.3		67	24.3		
2009	39	13.8		29	10.5		
Gender							**<0.001**
Male	242	81.2		180	66.4		
Female	56	18.8		91	33.6		
Knowledge of study							**0.350**
Excellent	101	34.5		94	34.9		
Very Good	134	45.7		130	48.3		
Partial	58	19.8		43	16.0		
None	0	0.0		2	0.7		
Consent							**0.217**
No	4	1.4		1	0.4		
Yes	288	98.69		265	99.6		
Contact information							**0.077**
No	6	2.0		1	0.4		
Yes	288	98.0		268	99.6		
Consent process was appropriate							**0.478**
Appropriate	294	100.0		268	99.6		
Inappropriate	0	0.0		1	0.4		
Satisfaction with CTRC							**0.214**
High	278	96.2		258	97.7		
Moderate	11	3.8		6	2.3		
Low	0	0.0		0	0.0		
Satisfaction with research staff							**0.824**
High	279	95.9		253	95.8		
Moderate	12	4.1		10	3.8		
Low	0	0.0		1	0.4		

Abbreviation: CTRC, Clinical and Translational Research Core

graphic features and specific clinical trial understanding of oncology patients to those without a cancer diagnosis. Patients with cancer were generally older than those enrolled in studies for other diagnoses, which is not surprising given that cancer tends to develop later in life. Oncology patients had inferior understanding of clinical cancer trials when compared to patients with other diagnoses. The reason for this is not clear. Oncology trials tend to be complicated in methods, potential side effects, and drug administration schedules, which could increase the likelihood that subjects might struggle to understand the information presented to them.

If informed consent standards are rigorous and understanding of the study itself is often inadequate, how can we help ensure that subjects comprehend as well as possible the methods, risks, benefits, and rights to choose or refuse participation? Other investigators have provided enhanced educational materials and modalities in hopes of optimizing this process. Specifically, a discussion with a research nurse via phone, face-to-face interviews, simplified consent forms, computer-based presentations, videotaped presentations, administering a quiz and then reviewing responses with participants, and utilization of the teach-back method in informed consent discussions (ie, asking the potential subject to summarize the key elements of the study in his/her own words) all have been tried with variable success.[12-14] Having a study staff member or educator spend additional time discussing a clinical trial with the subject appears to be slightly more effective than the other aforementioned options. Further research is needed to identify an efficient means of effectively increasing clinical research subjects' knowledge of the trials in which they participate, particularly for oncology patients and others receiving complex, high-level care.

There are limitations to our study. The questionnaire administered during subject interviews was not validated. Although the 2 advocates and the nurse manager conducting the interviews asked the same questions of each subject, interpretation of subjective questions—namely, those delving into level of understanding—probably varied between the 3 interviewers. Administration of study questions verbally also may have been a limitation in that subjects may not have openly provided feedback because of concerns that their response may affect the quality of their care. The medical and psychological status of subjects were not screened or evaluated, and these factors could affect participants' understanding of study aims, methods, and risks. Finally, specific concepts subjects found difficult to grasp, such as randomization and the goals of phase 1 trials, were not recorded. We therefore cannot comment on what aspects of clinical trials should be covered more thoroughly when educating participants.

CONCLUSION

In summary, our study shows excellent compliance with consent requirements by research teams on our clinical research unit. The level of subjects' knowledge of research is quite respectable, particularly among those participating in nononcology studies. The level of knowledge decreases in the subjects above age 60. The study documents the need for greater effort to inform oncology and older subjects about research protocols.

Table 4. Descriptive Statistics by Age Group, with Fisher's Exact Test *P*-values

	Ages 20-40 Years			Ages 41-60 Years			Ages 60 Years or Older			
	N	Mean/%	SD	N	Mean/%	SD	N	Mean/%	SD	*P*-value
Age	**95**	**26.23**	**7.26**	**200**	**53.24**	**5.11**	**275**	**69.47**	**6.33**	**NA**
Year of visit										**0.170**
2005	4	4.3		19	9.7		34	12.9		
2006	21	22.8		58	29.7		75	28.4		
2007	28	30.4		49	25.1		64	24.2		
2008	21	22.8		48	24.6		61	23.1		
2009	18	19.6		21	10.8		30	11.4		
Gender										**0.061**
Male	47	49.5		107	53.5		117	42.7		
Female	48	49.5		93	46.5		157	57.3		
Knowledge of study										**<0.001**
Excellent	40	42.6		79	40.3		76	27.8		
Very Good	47	50.0		94	48.0		123	45.1		
Partial	7	7.4		22	11.2		73	26.7		
None	0	0.0		1	0.5		1	0.4		
Consent										**0.225**
No	2	2.1		2	1.0		1	0.4		
Yes	93	97.9		193	99.0		268	99.6		
Contact information										**0.883**
No	1	1.1		3	1.5		3	1.1		
Yes	93	98.9		196	98.5		268	98.9		
Consent process was appropriate										**1.000**
Appropriate	94	100.00		199	100.00		270	99.6		
Inappropriate	0	0.0		0	0.0		1	0.4		
Satisfaction with CTRC										**0.798**
High	90	97.8		187	97.4		260	96.3		
Moderate	2	2.2		5	2.6		10	3.7		
Low	0	0.0		0	0.0		0	0.0		
Satisfaction with research staff										**0.569**
High	89	97.8		188	95.9		256	95.2		
Moderate	2	2.2		7	3.6		13	4.8		
Low	0	0.0		1	0.5		0	0.0		

Abbreviation: CTRC, Clinical and Translational Research Core

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