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Are Subjects Satisfied with the Informed Consent Process? A Survey of Research Participants

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ABSTRACT. ***Objective.*** Letters of information (LOI) for clinical trials are becoming longer and more complicated. We investigated patients' perspectives of their ability to understand the information presented during a clinical trial. Satisfaction with and motivation for participation in clinical trials were also ascertained. Perceptions from various treatment disciplines were compared.

Methods. Participants were chosen from 14 clinical trials (departments of rheumatology, ophthalmology, and cardiology) conducted at the same university. Subjects were asked to complete a written questionnaire that assessed demographic information, recall and understanding of information, subjects' decisions to participate, and perceptions/opinions of the study. The response rate was 75% (rheumatology, n = 74; ophthalmology, n = 32; cardiology, n = 84).

Results. The majority of respondents (98%) indicated that they were satisfied with the informed consent process and with their involvement in a trial (97%). Subjects who reported having understood the LOI had better recall of placebo/active drug comparator ($p < 0.03$), and better understanding of why placebo was used ($p < 0.04$). No differences were found between those who reported understanding and those who did not on understanding the concept of concealed allocation (blinding). Subjects who felt they had received "the right amount of information" were more likely not to understand concealed allocation. The most frequent reason for trial participation was to help medical science (80%). Subjects with higher education were more likely to understand the reason for placebo use ($p < 0.0003$), but were not more likely to understand concealed allocation ($p < 0.08$).

Conclusion. Subjects reported that they were satisfied with the informed consent process and their experience in a clinical trial, and that they understood trial concepts. Subjects may be able to self-assess their own level of understanding for trial concepts that intrinsically make sense within the context of their beliefs about medical care, but other trial concepts may be misunderstood/misinterpreted regardless of self-assessment of understanding or education level (i.e., concealed allocation). Subjects may prefer to believe that investigators know which treatment they are receiving, and have made a good treatment decision specific to their case, despite having being told about concealed allocation and placebo use. (J Rheumatol 2003;30:815–24)

Key Indexing Terms:
INFORMED CONSENT RANDOMIZED CONTROLLED TRIAL
PATIENT UNDERSTANDING

Letters of information (LOI) have become longer and more complicated as clinical trials have become more sophisticated. There has been debate whether the purpose of LOI has shifted from informing patients to protecting investigators and sponsors, as these forms are legal documents with liability clauses, and whether such a wealth of information is actually required to "fully" inform the patient without unnecessarily confusing or overwhelming him/her[1-4]. Although a subject has been adequately informed, it does not necessarily follow that the subject has satisfactorily understood the major study concepts (clinical uncertainty, random allocation, concealment, use of placebo, voluntary participation) that may often be obscured by technical and legalistic jargon. Studies in the literature have revealed the difficult readability of the patient LOI used in randomized controlled trials[5-7]. Subjects in clinical trials were found to be less than adequately informed and not appreciative of their rights and duties during the trial[1,5,8-11]. Other studies have examined simplifying or supplementing written consent documents with material to clarify trial concepts, yielding positive results[12-14]. It is concerning that subjects may enter studies unaware of possible risks, as well as their basic rights as voluntary subjects. The resulting direct or indirect physical, mental, or psychosocial effects may have

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the capacity to not only adversely influence study data, but also to introduce an element of distrust or lack of confidence into the physician-patient relationship[2,15,16].

Several studies using hypothetical randomized controlled trial (RCT) designs have been conducted with samples from members of the public, to determine if subjects would participate when provided the information[17-19]. Much of the research conducted with actual trial participants to retrospectively assess understanding of consent forms has been done within specific disciplines of medicine where patients' decisions may be adversely affected by the circumstances associated with the specific trial; for example, in acute care situations in which there are time constraints on the consent process (i.e., myocardial infarction[9,20-22], childbirth[23]), and in cases of patients who have psychiatric illness[24,25], or who are children, for whom a designee must provide assent for their participation in the trial[26,27]. There is also a large body of research on the consent process and trial participation in cancer clinical trials[28,29]. Other groups have conducted in-depth studies of subject perceptions of trial concepts[30-32]. However, there is a paucity of research on understanding (and patients' perceptions of) the consent process in clinical trials involving patients with chronic diseases, with the exception of a study by Ferguson[33], and no studies have specifically focused on the rheumatic diseases. Subjects with chronic illness may hold different views of their health status and may behave differently than those with more acutely life-threatening illnesses[34]. We assessed how these patients perceive clinical research. Additionally, due to the likelihood that many of these patients will be approached to participate in clinical trials at some point during the course of their illness, we felt that this question should be addressed.

We assessed (1) satisfaction with the level of information received through the informed consent process; (2) satisfaction with participating in a clinical trial; and (3) whether there were any obvious differences in the level of recall and understanding of trial information that may have contributed to decreased satisfaction, among patients who were previously (or who were concurrently at the time of this survey) involved in RCT in rheumatology. We surveyed subjects from 3 different disciplines [rheumatology, cardiology, and ophthalmology (glaucoma)] to obtain data to provide a broader viewpoint. Subjects' rationales for entering into trials and their general views on medical research were also ascertained. We hypothesized that as many trials have quite complicated LOI, subjects would lack comprehension of some elements of the study, and thus may be dissatisfied with the informed consent process to some degree. We believed that there could be differences in the levels of satisfaction among the 3 different disciplines (rheumatology, ophthalmology, cardiology), but that higher satisfaction (with both the informed consent process and the trial) would be positively correlated with a higher level of recall and understanding of trial information. We thought that level of education might influence understanding.

MATERIALS AND METHODS

Study design. This study was a survey in which a written questionnaire was mailed to 253 subjects who had previously participated in and/or who were concurrently (at the time of the survey) participating in RCT and who met the following criteria: (1) subject had received a letter of information; (2) subject had signed an informed consent document; and (3) the RCT involvement was less than 5 years ago. Subjects were all involved in trials taking place at the University of Western Ontario that had been approved by the University Ethics Board. The minimum and maximum time ranges between signing the consent form for the subject's respective trial and completing the study questionnaire were 2 months to 5 years. Questionnaires were sent out to all eligible subjects (including screen failures); however, due to low response by screen failures, these were not included in the final analyses. Nonrespondents were sent the questionnaire a total of 3 times. The response rate was 75% (74% rheumatology, 77% cardiology, 73% ophthalmology). The majority (92%) of participants were Caucasian (174) and 55% were female. No data were collected for analyses on nonrespondents.

The questionnaire was coded corresponding to the discipline of research. Data were categorized and entered into a database and descriptive statistics were performed. Possible confounders and between-groups analyses were performed using JMP statistical software.

Subjects were selected from the following areas of medical research: rheumatology (osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus trials), ophthalmology (glaucoma trials), and cardiology (coronary artery disease prevention) at UWO. All studies were double blinded (with one exception in ophthalmology) and were either placebo controlled or had active drug comparators or both. The majority of trials were phase III, multicenter trials sponsored by pharmaceutical companies (2 trials were not corporate sponsored). Subjects were not financially compensated for participation, with the exception of reimbursement for out-of-pocket expenses in some cases. Table 1 shows the number of respondents from each trial, as well as a summary of the trial design and information provided in the LOI. The study coordinators and investigators provided information about the standard procedures generally followed for the clinical trials included in this survey. These accounts are provided below, categorized by subspecialty.

Rheumatology trials. All participants from 10 trials were sent the questionnaire. The trial participants had the following diagnoses: rheumatoid arthritis (RA), 5 trials; osteoarthritis (OA), 3 trials; RA or OA, one trial; and systemic lupus erythematosus (SLE), one trial (Table 1). Two of the 10 trials were not industry sponsored: a randomized, double blind, placebo controlled study of glucosamine sulfate in patients with OA, and a randomized, double blind, placebo controlled study of methotrexate in patients with SLE.

For the conduct of the included trials: eligible subjects were identified through chart review or newspaper ads and screened by telephone contact, when the coordinator would briefly outline the study objectives, procedures, and time commitment. Interested patients were invited for a screening visit at which they were presented with the LOI and consent form. The discussion would begin with the study coordinator or nurse summarizing the study, emphasizing the key points (mainly to do with exclusion criteria or medication restrictions), and reiterating the time commitment. Supplementary information provided by the study coordinator and/or nurse was mainly obtained from the study protocol, and as such, would not differ from that provided in the written LOI. The physician commonly focused the discussion on the risks/benefits, study length, and randomization process as well as answering questions about the drug mechanisms and properties. A few subjects brought the LOI home to reread or discuss with others (family, general practitioner).

Ophthalmology trials. Patients who participated in glaucoma trials were identified from an ophthalmologist's practice. There were 3 trials in which participants had been involved: 2 were double blinded, placebo controlled studies, one of latanoprost and one of timoptic; the other was an unblinded

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Table 1. Information contained in the letter of information and informed consent forms for trial assessed through the questionnaire survey.

Investigational Treatment (Disease)	No. of Respondents	Comparator	Chance of Being on Placebo (%)	Explanation of Use of Placebo in Trials	Explanation of Random Allocation	Double Blinded	Explanation of Double Blinding
Rheumatology trials							
Glucosamine sulfate (OA)	7	Placebo	1 in 2 (50)	No	Brief	Yes	Yes
MK-0966 (OA)	9	Active drug	—	—	No	Yes	Yes
Celecoxib (OA)	10	Active (NSAID)	—	—	Yes	Yes	Yes
SC-58635 (OA & RA)	7	Active drug	—	—	Yes	Yes	Yes
D2E7 (RA)	13	Placebo	1 in 5 (20)	No	Brief	Yes	Yes
Metgo (RA)	1	Placebo	1 in 2 (50)	No	Brief	Yes	Yes
COX 189 (RA)	8	Placebo + active drug	1 in 6 (13)	No	Yes	Yes	Yes
Trocade (RA)	7	Placebo	1 in 5 (20)	No	No	Yes	Yes
Valdecoxib (RA)	7	Placebo + active drug	1 in 5 (20)	No	Brief	Yes	Yes
SMILE (SLE)	5	Placebo	1 in 2 (50)	Yes	Yes	Yes	Yes
Ophthalmology trials							
Latanoprost safety study	12	Active drug	—	—	No	No	No
Latanoprost	8	Placebo	1 in 2 (50)	No	No	Yes	Yes
Timoptic	12	Placebo	1 in 3 (33)	No	No	Yes	Yes
Cardiology trials							
HOPE Study	84	Placebo	1 in 2 (50)	No	No	No	No

OA: osteoarthritis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus.

safety trial of latanoprost (Table 1). Participants in the safety trial were excluded from the analyses relating to concealed allocation. The study coordinator would summarize the study and procedures and reiterate the key points using information from the LOI and study protocol during the discussion.

Cardiology trial. All participants from cardiology had been involved in one clinical trial, the Heart Outcome Prevention Evaluation study (HOPE). Subjects were aged 55 years or older and had clinical evidence of vascular disease or were at high risk of developing complications of coronary disease, myocardial infarction, or stroke at the time of recruitment into the study. This was a randomized, double blinded, placebo controlled trial in which subjects had a 50% chance of receiving the study drug ramipril (Altace) versus placebo, with or without vitamin E (Table 1).

The discussion about trial entry was usually initiated by the physician, who would explain the study including the purpose of the trial, why it was required, and how it would affect the subject, and then introduce the study coordinator, who would cover details including the timetable of events, study procedures, and restrictions. The physician would answer remaining questions. Subjects who had not participated in a previous trial were also given an explanation about clinical trials — that clinical uncertainty results in the need for experimentation — and were provided with information about the approval process required before initiating research with human subjects.

The questionnaire. A questionnaire was devised to assess (1) patients' overall perceptions of the trial and the consent process, (2) recall of information presented during the consent process, and (3) the level of understanding of the trial concepts (concealed allocation, use of placebo). (For this study, concealed allocation, or blinding, was defined as the investigator and subject both being prevented from knowing with certainty which treatment the subject was receiving; placebo was defined as an inactive substance identical to study drug.) The 4 page questionnaire had a total of 39 items beginning with a short demographics section (sex, age, education level, ethnicity, type of illness, prior participation in trials) followed by questions on specific aspects of the RCT, including whether the subject received a letter of information and signed a consent form; recall and understanding of (1) the chance of allocation to placebo, (2) study drug comparators, and (3) the reason for using placebo; whether the subject knew what drug he/she was receiving, whether the subject thought the investigator knew what drug he/she was taking, and what drug the subject believed he/she was taking. With the exception of one open-ended question ("Why do you think we use placebo as a comparison treatment?"), all the above questions were multiple choice format. The correct answers for chance of treatment allocation were protocol-specific.

The next section asked subjects to indicate factors that influenced their decisions to participate in the trial as well as to indicate reasons why they thought their physician might participate in research studies. The last section used a 4 point scale to assess the patients' perspectives and level of satisfaction with aspects of trial participation including: whether the subject felt he/she understood the information, length of the LOI, time commitment, time spent with study doctor or research staff, whether enough time and information had been provided orally in the discussion period(s), the expectation to get better, whether the subject felt that research with the goal of learning about new drugs was important, participation in future studies, and overall satisfaction.

RESULTS

Subjects from rheumatology, ophthalmology, and cardiology differed significantly on demographic variables, including sex, age, and highest level of education (Table 2). With the exception of education level, these variables were found not to have significantly confounded responses on satisfaction, recall, or understanding. The time interval between signing the trial consent form and completing the study questionnaire did not significantly affect responses on questionnaire items, with the exception of ability to remember receiving a letter of information. All subjects who signed consent forms < 1 year before filling out the questionnaire remembered receiving it, in contrast to those who signed consents > 1 year before, with 31 out of 162 subjects not remembering receiving the LOI ($p < 0.001$).

Satisfaction with the informed consent process/trial involvement. The majority of participants (98%) indicated that they were satisfied with the informed consent process (100% rheumatology, 96% ophthalmology, and 97% cardiology).

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Table 2. Demographics of participants reported as number (%) of responders (% is of total within each group). There were more women in the rheumatology trials and more men in cardiology research ($p < 0.0001$). The rheumatology subjects were younger than the other groups ($p < 0.0001$), and had the highest level of education ($p < 0.0082$).

Study	Participants	Cardiology	Rheumatology	Ophthalmology	p
N	190	84	74	32	
Sex					
Female	106	25 (30)	61 (82)	20 (63)	0.0001
Male	84	58 (70)	13 (18)	12 (37)	
Age, yrs, median (range)	63 (22–84)	70 (55–84)	54 (22–80)	70 (46–84)	0.0001
Education					0.0082
Elementary	35	24 (29)	3 (4)	8 (25)	
High school	86	37 (44)	36 (49)	13 (41)	
Higher education	69	23 (27)	35 (47)	11 (34)	

Of the total respondents, 93% felt that they had been given the correct amount of information and 95% reported having been given enough time to read the LOI and consent form. However, 16% of total respondents reported that they thought patients had been given too much information, and 18% admitted to not having fully read the LOI and consent form. Responses regarding the discussion of information continued to reflect subjects' positive attitudes, with the majority (97%) reporting that they had had sufficient opportunity to ask questions; 98% felt that the research staff had devoted enough time to providing answers to questions. However, 10% reported feeling "afraid to ask questions." Overall attitudes toward trial participation also tended to be positive, with 97% of subjects agreeing that they were satisfied with their involvement in the clinical trial. Ninety-seven percent of trial participants valued support for research into drug development, while 86% reported that they would be willing to participate in future clinical trials. Interestingly, 50% of subjects reported that they had "expected to get better" through participating in the study. Results are summarized in Table 3.

A Likert-type scale rating participants' agreement to statements about perceptions/attitudes toward clinical trials and informed consent was used in our questionnaire. As most subjects indicated similar opinions on several items, the between-groups analyses (agree vs disagree) resulted in unstable p value estimates due to insufficient numbers of observations at one end of the scale (indicated in Table 3). On those items where adequate analyses were performed, significant differences in responses from rheumatology, ophthalmology, and cardiology were observed for the following: (1) not having fully read the LOI, (2) feeling one had been given the correct amount of information, (3) the expectation to get better, and (4) feeling that study proce-

Table 3. Participants' (rheumatology, ophthalmology, cardiology) evaluations of satisfaction with components of the informed consent process and clinical trial involvement. Reported as number of subjects (%).

Statement with which Subjects Were Asked To Rate Their Level of Agreement or Disagreement	Strongly Agree	Agree	Disagree	Strongly Disagree
I understood the 'Letter of information' and the 'patient consent' form†	87 (47)	96 (52)	2 (1)	1 (< 1)
Patient information was too long	6 (4)	21 (12)	111 (66)	31 (18)
I did not fully read the 'informed consent' form*	12 (7)	19 (11)	74 (43)	67 (39)
I was given the right amount of infomation about the study*	84 (46)	87 (47)	12 (7)	1 (< 1)
I feel that I had enough time to read the 'letter of information' and consent form†	83 (46)	88 (49)	8 (4)	1 (< 1)
Overall, I was satisfied with the informed consent process†	77 (43)	100 (55)	3 (2)	0
I had sufficient opportunity to ask questions about the research study†	96 (52)	84 (45)	5 (3)	1 (< 1)
The doctor or the nurse took time to answer all of my questions†	119 (64)	63 (34)	1 (< 1)	2 (1)
The doctor or nurse gave me a clear explanation to all of my questions†	103 (56)	77 (42)	3 (2)	0
I was afraid to ask questions	8 (5)	9 (5)	68 (38)	92 (52)
I expected to get better by being in the study*	28 (16)	61 (34)	65 (37)	23 (13)
The study took a lot of extra time due to the various procedures*	9 (5)	37 (21)	91 (51)	42 (23)
All things considered, I was satisfied with my involvement in the study†	80 (45)	92 (52)	3 (2)	3 (2)
Research study's goal of learning about new drugs is important to me†	95 (53)	80 (44)	4 (2)	1 (< 1)
I will participate in other future research studies	64 (38)	82 (48)	18 (10)	6 (4)

* Responses (agree vs disagree) to these items differed significantly between groups (rheumatology, ophthalmology, cardiology), see Discussion. † Upon analyses of between-groups differences, responses (agree vs disagree) to these items produced unstable estimates of p values due to small numbers.

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dures "took a lot of extra time." Cardiology study subjects were more likely to admit not having fully read the LOI (27%), versus rheumatology (10%) and ophthalmology (16%) subjects ($p < 0.02$). Cardiology patients were also less likely to agree: (1) that they had been given the correct amount of information regarding the trial (88% cardiology agreed vs 97% each of rheumatology and ophthalmology; $p < 0.04$); (2) that they had expected to get better by participating in the trial (39% of cardiology vs 57% of rheumatology and 64% of ophthalmology agreed; $p < 0.02$); and (3) that the study involved a lot of extra time (15% of cardiology vs 38% of rheumatology and 27% of ophthalmology agreed; $p < 0.005$).

The main reasons cited for participation in trials were: (1) to help medical science (80%: rheumatology 79%, ophthalmology 76%, cardiology 82%); (2) to eventually help others (80%: rheumatology 84%, ophthalmology 66%, cardiology 83%); and (3) to improve one's condition (67%: rheumatology 86%, ophthalmology 79%, cardiology 46%). Study participants believed the study physician took part in clinical trials for the following reasons: (1) to gain scientific knowledge (92%: rheumatology 97%, ophthalmology 90%, cardiology 88%); (2) to benefit patients (91%: rheumatology 94%, ophthalmology 90%, cardiology 89%); (3) to gain access to new treatments (64%: rheumatology 77%, ophthalmology 73%, cardiology 51%); (4) to publish a paper (24%: rheumatology 34%, ophthalmology 13%, cardiology 18%); and (5) to make money (3%: rheumatology 5%, ophthalmology 0%, cardiology 2%).

Recall and understanding. The highest level of education obtained by study subjects was associated, although not significantly, with the ability to accurately report trial details (study drug comparator and chance of taking placebo), as those with a secondary school degree (or higher) tended to score better than those with elementary school. Subjects with post-secondary education were more likely to partially or fully understand (66%) why placebo was used in the clinical trial than high school (54%) and elementary school (22%) educated subjects ($p < 0.0003$). However, they did not score higher on items addressing comprehension of concealed allocation, and they tended to believe that they knew which drug they were taking even though they were participating in blinded trials (38% of university graduates, 35% of high school, 31% of elementary school graduates; $p < 0.8$).

Full understanding of the role of placebo in clinical trials (as assessed by an open-ended question: "Why do you think placebo is used for comparison in clinical trials?") was demonstrated by 13% of participants, 56% indicated a partial understanding, and 30% reported that they did not know. Overall, 76% of subjects were able to recall whether they had the chance of receiving placebo, and 39% were able to accurately recall their chances (i.e., 1 in 2, 1 in 3, etc.) of being allocated to take placebo. Cardiology subjects (49%) were more likely than rheumatology (20%) or ophthalmology (32%) subjects to respond correctly when reporting their chance of being allocated to placebo ($p < 0.013$). Overall, 64% of participants correctly recalled whether the study drug had been compared to active drug, placebo, or both. Rheumatology subjects were more likely to correctly recall whether the study drug comparator was active drug, placebo, or both ($p < 0.021$) (Table 4).

Table 4. Responses, reported as number of subjects, (%) of each group to questions assessed through the informed consent questionnaire. All trials were double blinded and placebo controlled. Some subjects were informed of their treatment allocation long after trial completion. Cardiology subjects knew best the chances of being allocated to placebo, whereas rheumatology subjects were correct more often in the comparison drug but underestimated their chance of being allocated to active drug. The ophthalmology subjects did not understand physician blinding as well as the others.

	Cardiology	Rheumatology	Ophthalmology	p
Did you know what drug you were taking during the study?				
Yes	34 (42)	24 (33)	17 (55)	0.2445
No	47 (58)	48 (67)	14 (45)	
Did you have a chance of being on placebo (sugar-pill)?				
Yes	66 (79)	58 (78)	20 (63)	0.6133
No	18 (21)	16 (22)	12 (37)	
If yes, what were the chances of being on the placebo treatment?				
Correct answer	41 (49)	18 (32)	5 (20)	0.0001
Incorrect answer	43 (51)	39 (68)	20 (80)	
Was the study drug compared to a placebo only, an active drug only, or was it compared to both an active drug and placebo?				
Correct answers	41 (49)	49 (66)	13 (41)	0.0103
Incorrect answers	43 (51)	25 (34)	19 (59)	
Do you think you were on an active drug?				
Yes (%)/Actual chance (%)	58/50	77/82	84/75	0.0007
Did you think the study doctor knew what drug you were on (active or placebo)?				
Yes	19 (24)	16 (23)	19 (68)	0.0001
No	60 (76)	54 (77)	9 (32)	

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Relationship between attitudes and recall/understanding. Subjects who had agreed that they "understood the LOI and consent form" tended to also correctly recall (although not significantly) trial details regarding chance of allocation to placebo, but they were significantly more likely to correctly report whether their respective trials had used active drug, placebo, or both as comparator(s) with the study drug (55% who understood LOI vs 0% who did not; $p < 0.03$) (Table 5). Two questionnaire items assessing subjects' understanding of concealed allocation addressed whether subjects "knew" which treatment they were on and whether they believed the study investigator "knew" which treatment they were on; in the LOI the meaning of "double blinded studies" had been explained (Table 1). No differences in understanding concealed allocation were found between subjects who agreed to having understood the written information and those who had disagreed ($p < 0.9$ and $p < 0.7$). However, subjects who had agreed that they understood the LOI were more likely also to have understood why placebo was used in the trial (51% of those who agreed vs 0% of those who disagreed; $p < 0.04$).

Those subjects who felt they had been given the "right amount of information" were not significantly more likely to correctly answer items assessing understanding of use of placebo or concealed allocation. They were, however, more likely to indicate that they "knew" which treatment they were on (36% who agreed vs 8% who disagreed; $p < 0.02$). This view is inconsistent with a proper grasp of the concept of concealed allocation. Similarly, those who had been "satisfied with [their] involvement in the study" were not more likely to recall trial details or understand concepts than those who were dissatisfied, with the exception that satisfied subjects also reported that they "knew" which drug they were taking (38% vs 0%, satisfied vs dissatisfied; $p < 0.02$). Subjects who had been "satisfied with the informed consent process" did not differ from those who were dissatisfied on recalling trial details or understanding.

Participants who "expected to get better by being in the study" did not differ from those who did not expect to "get better" on recall items. Interestingly, approximately the same percentage of those who expected to "get better" and those who did not also stated that they (1) "knew" which treatment they were taking in the study (36% vs 38%, respectively; $p < 0.8$), and similarly, (2) they believed they were taking active drug (69% vs 67%; $p < 0.9$). However, subjects who expected to "get better" were also more likely to believe that the study physician "knew" which treatment they were taking (34% of those who expected to get better vs 17% of those who did not; $p < 0.01$). In addition, participants who were willing to take part in future trials were more likely to believe that the study physician knew which treatment they had been on (27% vs 5% of participants who were not willing to take part in future trials; $p < 0.01$).

Cardiology and ophthalmology subjects overestimated the likelihood that they were taking active study drug: 58% of cardiology (actual chance 50%) and 84% of ophthalmology (actual chance 75%) believed this to be the case, compared to rheumatology subjects, of whom 77% (actual chance 82%) believed they were on active medication, thus underestimating the chance. Subjects who believed they had been taking active drug were more willing than those who did not to participate in future studies (72% vs 50%; $p < 0.05$).

DISCUSSION

It is not surprising that the majority of respondents with chronic diseases (> 93%) reported feeling satisfied with their involvement in the trial, and the information provided (written and oral), and indicated that they understood the concepts presented in the LOI and held positive attitudes toward medical research. Ferguson found similar results in a study in which patients' perceptions of the adequacy of the information provided to them (prior to participating in a clinical trial for their chronic illness) was obtained via interview, whereby the majority of subjects reported that the information had been adequate and understandable. Actual understanding/recall of information was not assessed[33]. Subjects who have participated in trials often feel that the experience has been positive[35-37], possibly due to a number of different factors. These may include increased attention/care from the study physician and research staff, as well as the hope of improving taking a new medication. As subjects in this survey study had agreed to participate in a clinical trial, the sample may have been biased toward patients who hold a more liberal or positive attitude toward medical research. Our study could have been strengthened by also having compared the perceptions of patients who had declined participation in the trials.

It is difficult to quantitatively assess how much information a patient understands through a written questionnaire. Dunn and Jeste have discussed this difficulty, whereby understanding, recall, and other terms may be less than adequately defined and used interchangeably in studies[14]. Our questionnaire primarily used multiple choice and a Likert-type scale, as open-ended questions introduce

Table 5. Responses to some of the questions asked in the questionnaire (results reported as number of responses).

	Yes	No	Can't Recall
Aware of participating in a trial	187	2	1
Received a letter of information	164	2	24
Signed an informed consent	159	1	29
Fully read the letter of information	31	159	—
Thought they knew what kind of medication they were taking	75	100	9
Correct answer given for a chance of being on placebo in particular trial	144	29	17

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another level of subjectivity into the analyses due to researcher interpretation. Ideally, an in-depth interview should be used to assess understanding, allowing the subject's ideas of the study concepts to be clarified as required. We addressed concealed allocation (blinding) and use of placebo. Other trial concepts were not assessed. We assumed that subjects who had a better understanding of the trial would be more likely to recall details as well as concepts involved in clinical trials.

Some studies negate self-report of understanding consent forms as a valid measure of actual understanding, as subjects may overestimate their level of understanding compared to the actual level[8,16,28,35]. In our study, subjects who felt they understood the LOI actually did demonstrate increased understanding of placebo use ($p < 0.03$), but were not significantly more likely to score better on items of recall ($p < 0.2$) or understanding of concealed allocation ($p < 0.7$). Similarly, satisfied subjects were not more likely to correctly recall trial details or understand trial concepts, and in some cases, demonstrated less understanding of concealed allocation.

An interesting trend emerging from our data suggests that those who felt themselves more informed or more satisfied with the information provided/trial process may actually have been more likely to misunderstand (or ignore) the concept of concealed allocation. Study participants who felt that they had received the "right amount of information" as well as those satisfied with [their] involvement in the study were each more likely to have reported that they "knew" which treatment they had received in the study ($p < 0.02$ for each) than those who had not felt the information adequate or who were dissatisfied with study involvement. The idea that subjects knew which treatment they had received (even though the LOI for the double blinded trials in which they had participated had stated that neither the patient nor the doctor would know the treatment) is inconsistent with the proper understanding of concealed allocation. It is possible that the satisfaction with the trial (and subsequent belief that one had been provided with adequate information) actually stemmed from the subject's belief that they knew which drug they were taking. The alternative hypothesis, however, is that subjects who are more satisfied have ignored or misunderstood the concept of blinding pertaining to their study treatment and may be more likely to misinterpret this information. It is apparent that subjects may struggle with the idea of concealed allocation. Other groups have described this phenomenon in-depth, whereby subjects had difficulty making sense of randomization[15,31,32]; our study supports their conclusions that subjects may have particular difficulty reconciling their own beliefs with concepts that seem counterintuitive, such as treatment not being determined by the physician.

Subjects' education level was associated with understanding the concept of placebo use (higher level education understood better; $p < 0.0003$), but they did not understand concealed allocation, and even tended to believe they knew which drug they were taking ($p < 0.8$). Higher levels of education have been associated with increased understanding in other investigations[3,12,38,39]. However, we postulate that education level may be somewhat accurate in predicting concepts that are more "intuitive" or seem to make more sense (like using placebo to eliminate study bias), whereas concepts that are counterintuitive or contrary to the subject's beliefs may be difficult to grasp regardless of the subject's education level or perception of their own understanding. Featherstone and Donovan found similar results, whereby age and time after randomization were not associated with recall and understanding. Subjects demonstrated adequate recall/understanding of trial details but had difficulty with the concept of random allocation, defined as allocation (to a treatment arm) by clinical researchers based on randomization schedules[15].

The LOI provided to study participants explicitly stated that subjects were not guaranteed any resulting change in their disease/health status through participating in the study. In spite of this, however, 50% of subjects reported that they had expected to get better by being in the study. Seventy percent overall believed they had been taking active drug (actual chance of active, 67%). Most patients would agree that physicians are hesitant to subject patients to unnecessary procedures, and so study subjects may find it difficult to believe that their doctor would suggest they enroll in a trial, undergo all types of assessments, and yet have no guarantee of benefiting from the study treatment. Edwards, *et al* found the phenomenon whereby subjects' cited self-interest as their main reason for participation to be in contrast to the fact that they had been told that they would gain little personal benefit through the trial, thus indicating a lack of understanding[16].

In our study, even though participants were told that the studies were double blinded, 29% thought the study doctor knew what kind of medication they were taking. It seems study participants want to believe the investigator knows the intervention, and thus can alter treatment for the best possible outcome. An intrinsic element of the doctor-patient relationship involves the trust and confidence a patient has for the physician's ability and the certainty that the doctor will act in the patient's best interest. Interestingly, in our study, subjects who "expected to get better" versus those who did not were not more likely to agree that they knew which treatment they were receiving or that they believed they were taking active drug, but they were significantly more likely to believe that the study physician knew which drug they were taking ($p < 0.01$). Subjects, in general, tend to invest much confidence in the study physician[1,15,40,41], as they indicated the physician's knowledge was associated with their expectations to improve, whereas their own beliefs about what drug they were taking were not. Other

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reports describe expectations that the doctor would assign them to treatment on a per-case basis, for which Dunn and Jeste coined the term "the therapeutic misconception"[14,15,32,40]. Others found that subjects initially trusted the study physician, but 50% developed distrust through their trial experience[15].

Participants cited they thought their study doctor participated in clinical trials to gain scientific knowledge (92%) and to benefit patients (91%), while 24% cited to publish a paper, and just 3% thought the physician participated to make money. We can conclude that subjects tend to believe the physician participated in the trial for the subject's best interest, in contrast to the physician's own self-interest (i.e., financial reimbursement, furthering credentials, etc.). Edwards, *et al* reported that 26–70% of patients or members of the public believed that physicians participated in trials even if equipoise was not present[16]; our results may have been different had we included the perceptions of individuals who did not agree to trial participation.

Overall, subjects slightly underestimated the chance of being allocated to active drug by 10%. Placebo chance could be overestimated because a subject participating in a trial may have an inherent expectation of receiving active treatment regardless of the odds. This may be similar to purchasing lottery tickets, expecting to beat the odds and win. Rheumatology subjects tended to underestimate their chance of receiving active drug (the other groups overestimated). We did not assess disease duration in this study; however, if disease duration was significantly greater in rheumatology subjects, it may support that there were more past treatment failures in rheumatology subjects than the others, thereby lessening their chances of improving.

Cardiology patients reported significantly different attitudes on several items compared to the others. They were more likely to admit they had not read the LOI ($p < 0.03$), and were less likely to agree that they had been given the correct amount of information ($p < 0.04$), that they had expected to "get better" ($p < 0.02$), and that the study involved a lot of extra time ($p < 0.005$). There are a number of possibilities for the difference in perceptions. As it was impossible for us to eliminate interdiscipline differences, cardiology patients may have been presented with more information or the trial design itself may have contributed toward these differences (especially since only one trial was assessed in cardiology vs multiple trials in the other groups). The effects of mood and personality traits on subjects' perceptions were not assessed in this study. Other studies have found that factors (mental state, seriousness of disease) may be associated with decreased recall in surgery patients[1,43]. It may be that differences between groups were due to intrinsic traits of the subjects within the subspecialties. Additional research would be required to conclusively determine any causal factors.

Although overall satisfaction with participation in clinical trials was observed in this study to be quite high, some of our findings were concerning: (1) 18% of participants admitted not reading the entire informed consent before signing it; however, recall of the information and the feeling of being properly informed was similar in both those who had and had not read the LOI; (2) 16% of participants felt they had been given too much information; and (3) 10% reported that they were "afraid to ask questions." Although the numbers here are relatively low, we have concern that these may be underestimates, as subjects knew the questionnaires would be assessed by research staff and may have underreported in responses to certain items.

The majority of subjects cited that their most common reasons for participation in clinical trials were: (1) "to benefit other patients" (80%) and (2) "to help medical science" (80%). Improvement of subject's own condition was the third most common reason (67%). Some studies have demonstrated a sense of altruism as part of subjects' motivation[8,23]. In contrast, Edwards, *et al* found self-interest to be the major reason for participation in the majority of the trials they reviewed[16]. In addition, we found (not surprisingly) that subjects who believed they had been taking active drug (vs those who did not) were more likely to be willing to participate in future studies ($p < 0.05$).

A limitation of our study is that we performed between-groups analyses on subjects who had obtained different LOI and had different time intervals from signing the consent to completing this survey study. Assessing the readability of the LOI and controlling for any significant differences would have strengthened this study; however, all LOI were approved by the same ethics board, with consistent information being included (such as protection of privacy, alternative treatments, etc.). Another limitation that may affect ability to recall/understand information was that some subjects were still completing ongoing trials; concepts and details would have been currently relevant to the subject, as opposed to those who had participated previously. Subjects could have referred to their original LOI to answer the questionnaire, also contributing toward perceived recall/understanding. Some trials included in this survey had multiple consent forms (e.g., following study amendments); this may have contributed toward increased recall. We have included data from individuals in a real-life context, who were not aware they would be asked to complete the survey at the time of consent to their respective trials, in contrast to a hypothetical situation.

Our subjects were primarily English–speaking Caucasians at a university health center. Thus, our conclusions may not be generalizable to other more varied populations. However, as we included subjects of 3 different subspecialties of chronic care, the results may describe more general trends among patients with chronic diseases. We questioned the research coordinators to ensure that trial procedures at the 3 different sites followed a basic format.

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No exceptional differences were noted between sites. Most trials in this study were sponsored by pharmaceutical companies. We cannot comment on any potential differences between perceptions to pharmaceutical and peer reviewed studies (which have less legal need for complicated LOI), but it would be interesting to address this question in the future.

We determined general perceptions of trial participants with chronic diseases. Subjects in trials tend to have positive attitudes toward medical research as well as the procedures involved and consider themselves well informed. It is important that researchers ensure subjects appreciate the concepts, as asking subjects if they have understood the presented information may be insufficient. Particular attention needs to be paid to concepts that are intuitively contrary to the beliefs of most patients (i.e., concealed allocation, clinical uncertainty), as even those with increased education or who believe they understood the presented information may not understand these basic trial design elements. It has been suggested in other reports that concepts contrary to the regular doctor-patient relationship should perhaps be focused on more intently when providing information for potential clinical trial participants[44,45]. We agree with this, as on some level, subjects may maintain their previously held beliefs in the doctrine employed in patient care, not making the full distinction between therapeutic clinical care and research.

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