CLINICAL SCIENCE

Motivation and frustration in cardiology trial participation: The patient perspective

Silmara Meneguin,[I] Luiz Antônio Machado César[II]

[I]University Estadual Paulista, Botucatu School of Medicine, Department of Nursing, Botucatu/SP,Brasil. [II]Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (INCOR), Departamento de Cardiopneumologia, São Paulo/SP, Brazil.

OBJECTIVE: The participation of humans in clinical cardiology trials remains essential, but little is known regarding participant perceptions of such studies. We examined the factors that motivated participation in such studies, as well as those that led to participant frustration.

METHODS: Patients who had participated in hypertension and coronary arterial disease (phases II, III, and IV) clinical trials were invited to answer a questionnaire. They were divided into two groups: Group I, which included participants in placebo-controlled clinical trials after randomization, and Group II, which included participants in clinical trials in which the tested treatment was compared to another drug after randomization and in which a placebo was used in the washout period.

RESULTS: Eighty patients (47 patients in Group I and 33 patients in Group II) with different socio-demographic characteristics were interviewed. Approximately 60% of the patients were motivated to participate in the trial with the expectation of personal benefit. Nine participants (11.2%) expressed the desire to withdraw, which was due to their perception of risk during the testing in the clinical trial (Group I) and to the necessity of repeated returns to the institution (Group II). However, the patients did not withdraw due to fear of termination of hospital treatment.

CONCLUSIONS: Although this study had a small patient sample, the possibility of receiving a benefit from the new tested treatment was consistently reported as a motivation to participate in the trials.

KEYWORDS: Motivation; Clinical trials; Frustration; Cardiology.

Meneguin S, César LA. Motivation and frustration in cardiology trial participation: The patient perspective. Clinics. 2012;67(6):603-607.

Received for publication on February 28, 2012; **First review completed on** February 28, 2012; **Accepted for publication on** March 2, 2012

E-mail: dcllucesar@incor.usp.br

Tel.: 55 11 26615387

INTRODUCTION

Clinical research is responsible for current scientific progress in the medical field, and the participation of human patients is vital for the confirmation of new therapeutic strategies.

Despite the efforts to ensure ethical rigor in research over the past 60 years, ethical concerns have been an area of concern to both researchers and government agencies, as studies may involve the participation of potentially vulnerable populations, especially in developing countries. Ethical issues are evoked in such studies, as the study investigators or sponsors are from developed countries, and the clinical trials are often conducted in developing nations.

Study participants are vulnerable due to their poor education level, unfamiliarity with scientific jargon, poverty, and general lack of access to health care services (1). Individuals with reduced autonomy, that is, those who are vulnerable, must be protected so that they are not used only as objects with which to conduct research and to aid in scientific development (2).

Although participant autonomy is facilitated by the use of an informed consent form in accordance with the Helsinki Declaration, and, in Brazil, with Resolution 196/96 (3), many studies have questioned the effectiveness of informed consent documents as the common clarification method used in clinical trials (4).

Such concern has arisen because many patients are incapable of understanding the details in the document presented to them (5) and often consent as a result of the socioeconomic conditions under which they live and the role that clinical trials play in their search for solutions to health problems (6). Under these circumstances, participants may become frustrated due to a lack of understanding of the actual role of a trial in which they have consented to participate.

Studies have shown that the decision to participate in a clinical trial is mainly motivated by altruism, that is, the possibility of helping other people and science (7-9), as well as by the desire for personal benefits, such as access to better care or treatment (10).

No potential conflict of interest was reported.

Nevertheless, little is known regarding the factors that motivate participation in cardiology clinical trials focused on heart failure (11,12). This study was conducted to evaluate the factors that motivate participation in cardiology clinical trials, as well as those leading to participant frustration.

METHODS

The present study was a descriptive, exploratory, and quantitative study conducted in a public hospital specializing in cardiology. The study protocol was approved by the Universidade de São Paulo Hospital das Clínicas Ethics Committee (reference number 1223/2005) on January 26, 2006, in accordance with the National Ethics Committee of the Brazilian Ministry of Health (3).

The following were established as inclusion criteria: age between 20 and 80 years; participation in phase II, III, or IV clinical trials for drug testing that were conducted in outpatient units from 2002 to 2006; placebo usage in the washout phase or that was compared to the tested drug; randomization into the clinical trial and consent to participate. Individuals who did not have the ability to remember their participation in the selected clinical trials and/or did not agree to participate in this study were excluded. Two groups were then formed: Group I, comprising patients who had participated in placebo-controlled trials after randomization, and Group II, comprising patients who had participated in clinical trials in which the tested drug was compared to another drug after randomization and in which the placebo was only administered during the washout period. The participants in both groups had the same clinical profiles, had chronic coronary arterial disease, and had been followed as outpatients at the institution. Some of these trials were published with all patients here enrolled (13,14) and other were part of the casuistic of the final trial (15).

Data were obtained by consulting patient ambulatory records and by conducting an interview with patients via a questionnaire containing 29 items that had been previously designed and developed after considering all of the items on the consent form necessitated by Resolution 196/96.

The questionnaire comprised two parts. The first part aimed to collect identifying and demographic information of the participants, such as name, hospital registration number, age, gender, marital status, occupation, time of follow-up at the institution, study in which he/she participated and whether he/she completed the study. In addition to general participant characteristics, this part of the questionnaire evaluated education according to the following levels: 1) elementary school, 2) secondary school and 3) college. This evaluation considered whether each of these levels had been completed.

The second part of the questionnaire consisted of open and multiple-choice questions concerning participation in the clinical trial. It began with questions related to the invitation and motivation for participation (Why did you choose to accept the invitation to participate in the study?; five answer choices: a) for the sake of science, b) for your own benefit, c) because the doctor assisting you asked you to do so, d) because the doctor said it would be good for you and e) for fear of not being given care or missing a treatment opportunity due to the fact that the study took place at a public hospital, or due to other reasons).

In the questionnaire, there were yes/no questions concerning information that must be included in a consent form, such as the importance of the study in which one was invited to participate, risks and inconveniences, the existence of other therapies, information confidentiality, expense refunds, compensation in the case of occasional damage or problems, the need to read the consent form before signing it, discussion about the consent document with the researcher, confirmation of comprehension of the information in the document and confirmation of comprehension of the word placebo.

Next, the questionnaire asked whether the participants had considered withdrawing from the study, with yes or no as possible answers. If the answer was affirmative, they were asked for their reason and to state why the researcher had not been informed, as all of the participants did complete the study. Finally, we asked the participants, in an open-answer format, what it meant for them to participate in a clinical trial. All questionnaires were answered by the patients themselves without any influence but with the help, when necessary, of one investigator. The same investigator aided all participants who required help.

Casuistic: Of the 106 participants selected for the interview, two had died prior to the interview, eight were excluded, two refused to participate, five did not come on the scheduled interview date, and nine were unable to be reached. Overall, 80 participants comprised the study sample of 60 males (75.0%) and 20 females (25.0%). Of those participants, 47 were in Group I (mean age 58.3 years), and 33 were in Group II (mean age 59.4 years). All participants were interviewed during the second half of 2006. The socio-demographic characteristics of all participants are shown in Table 1.

Table 1 - Socio-demographic characteristics of the study sample.

Characteristics	Group				Total		p	Test
	I		II					
	n	%	n	%	n	%		
Gender								
Female	12	25.5	8	24.2	20	25.0	0.896	C
Male	35	74.4	25	75.8	60	75.0		
Education								
0-7 yr	32	68.0	19	57.6	51	63.8	0.606	L
8-10 yr	5	10.6	4	12.1	9	11.2		
11-14 yr	5	10.6	7	21.2	12	15.0		
15 + yr	5	10.6	3	9.1	8	10.0		
Marital status								
With a partner	40	85.1	24	72.7	64	80.0	0.180	C
Without a partner	7	14.9	9	27.3	16	20.0		
Employment activity								
No	19	40.4	23	69.7	42	52.5	0.010	C
Yes	28	59.6	10	30.3	38	47.5		
Employment status								
Onsickleave	1	2.1	0	0	1	1.2		
Retired	12	25.5	18	54.5	30	37.5	0.02	
Homemaker	6	12.8	5	15.2	11	13.8		V
Working	28	59.6	10	30.3	38	47.5		

C = chi-square test; L = Likelihood Ratio Test; V = Likelihood maximum test.

Statistical analysis

The quantitative variables were analyzed by the determination of means and standard deviations. The classificatory variables are presented in tables with absolute (n) and relative (%) frequencies.

To evaluate whether there was an association between the questions of interest, the Student's t test, the chi-square test, the likelihood ratio test or Fisher's exact test was used when applicable. Statistical analyses were performed using SPSS Version 15.0 (SPSS Inc., EUA), and the level for significance was set at $p<0.05$.

Qualitative analysis

The content analysis methodological framework was used to analyze the descriptive data obtained by means of the open questions (16).

Initially, pre-analysis, which consisted of the content organization phase and was aimed at systematizing ideas, was conducted. Next, the texts that essentially involved the operation for data categorization was explored. Finally, the data were analyzed and interpreted.

RESULTS

In both groups, most of the participants were illiterate or had an incomplete elementary school education (63.8%), thus characterizing the overall sample as having a poor education level. Sixty-four (80.0%) participants had a partner and were either married or had a common-law relationship.

Regarding employment, half of the participants (51.3%) did not have a formal job, with 37.5% retired and 13.8% performing household activities.

When the participants were asked about their reason for participating in a clinical trial, 53 subjects (66.2%) in the combined groups cited the personal benefit expected as the primary reason, followed by the sake of science 34 subjects (42.5%) (Table 2).

It was also found that 25.0% of the participants participated in the clinical trials due to their doctor's request or to recommendations to participate in the clinical trial, indicating the influence of professionals in the decision-making process. Other individuals participated in the trial because it was conducted at a public hospital (10.0%) and because they feared no longer being given care at the institution (3.8%) if they refused. Other cited reasons, which represented 6.2% of the responses, were related to the possibility of clinical tests that would not be available during routine hospital care and to the influence of their participation on the care received.

Nine patients (11.2%) reported the desire to withdraw from the clinical trial (Table 3), but they did not inform the investigator and completed the trial.

The main reason that led individuals from Group I (6.4%) to consider withdrawing was the risk involved in certain tests during the trial. In Group II, the main cited reason for considering withdrawal was the frequency of medical consultations required (6.0%).

The main reason reported by the participants for not having interrupted their participation in the clinical trial was fear of being prevented from receiving care at the institution and discontinuation of their treatment (5%).

Additionally, it was found that the attempt to find a treatment to improve their heart condition led the participants to not withdraw from the study despite their dissatisfaction (2.5%).

DISCUSSION

Clinical research with pharmaceutical industry fund in Brazil is still a relatively new area of concern, and it was only in 1996 that guidelines and regulating standards for studies involving humans were approved (3). Consequently, the number of clinical studies sponsored by pharmaceutical companies increased (particularly in cardiology), which was

Table 2 - Factors associated with the decision to participate in the clinical trial.

Reasons	Group						*p*	Test*
	I		II		Total			
	n	%	n	%	n	%		
For the sake of science	26	55.3	20	60.6	46	57.5		
No							0.638	C
Yes	21	44.7	13	39.4	34	42.5		
For your own benefit								
No	17	36.2	10	30.3	27	33.8	0.585	C
Yes	30	63.8	23	69.7	53	66.2		
Because the doctor assisting you asked you to								
No	42	89.4	30	90.9	72	90.0	1.000	F
Yes	5	10.6	3	9.1	8	10.0		
Because the doctor assisting you said it would be good for you								
No	39	83.0	29	87.9	68	85.0	0.752	F
Yes	8	17.0	4	12.1	12	15.0		
For fear of not being cared for at the hospital								
No	45	95.7	32	97.0	77	96.2	1.000	F
Yes	2	4.3	1	3.0	3	3.8		
Because it was a public hospital								
No	41	87.2	31	93.9	72	90.0	0.459	F
Yes	6	12.8	2	6.1	8	10.0		
Others								
Não	44	93.6	31	93.9	75	93.8	1.000	F
Yes	3	6.4	2	6.1	5	6.2		

C = chi-square test; F = Fischer's exact test.

Table 3 - Participants who thought about withdrawing from the clinical trial.

Did you think about withdrawing from the study?	Group				Total		*p*	Test*
	I		II					
	n	%	n	%	n	%		
No	42	89.4	29	87.9	71	88.8	1.00	F
Yes	5	10.6	4	12.1	9	11.2		

F = Fischer's test.

mainly due to the prevalence of diseases and large population found in developing countries, easy recruitment and good clinical research centers (17).

This increasing number of clinical research has been a source of concern because the participants in clinical trials in these countries may be more vulnerable during the consent process due to their socio-economic conditions, poor education level and limited access to health care services (18). All of these issues were observed in the present study.

Regarding the factors associated with the decision to participate in these studies, the expectation of personal benefit and altruism were the main motivating factors.

Our results are similar to those of an Israeli study by Yuval et al. (19) of 150 patients who participated in a randomized and double-blinded clinical trial of a drug developed for acute myocardial infarction. The study revealed that 43% of the patients participated in the study to receive better treatment, 12% expressed a desire for a good follow-up, 35% reported a desire to help promote medical research, 14% did not report a definite reason, and 8% reported being afraid to refuse to participate.

The expectation of personal benefit from participation in the clinical trial is considered to be the major determinant of successful patient recruitment (20).

However, when a participant erroneously believes that a study can offer substantial clinical benefit, a therapeutic misconception arises (21). In this situation, a patient who understands that his/her doctor's main goal is to find the best treatment for his/her disease may overestimate the personal therapeutic benefit from participating in the study. Nevertheless, these trials can produce a large amount of useful scientific knowledge and provide important benefits to future patients even if they do not provide a direct benefit to the current participants (22). Additionally, as an investigator, a doctor makes treatment decisions based on the specific design of each study (23).

However, many patients, as exemplified by this study, also participate in clinical trials because they are motivated by altruism, which corroborates the findings from other studies, particularly oncological and prevention studies (11,24). In ethical terms, such an attitude is ideal, as the participant's individual benefit cannot be guaranteed, nor is that the objective of a clinical trial (24).

Burguess et al. (25) interviewed 250 patients who participated in cardiovascular clinical trials and observed that the main cited reasons for participation were the possibility of access to medical care and a desire to contribute to the advancement of science. Another point of interest in our study is that 25% of the participants participated in the clinical trial because of a doctor's request or recommendation. This information reflects the influence that a doctor's recommendations can have on a patient's life trajectory and on his/her decision-making process (26). However, the fact that people tend to change their behavior when they are the targets of interest and attention, regardless of the specific nature of an intervention, must also be considered. This phenomenon is known as the Hawthorne effect (27), and in such situations, patients become eager to please their doctors and make them feel successful. Additionally, patients wish to participate so that ''good'' results can be achieved in the study.

Although the doctors who conducted the clinical trials and enrolled the patients in this study were not always the same as those who had cared for the patients in the institution's outpatient clinic, it is necessary to consider the potential conflicts of interest that exist in studies sponsored by pharmaceutical companies.

Nevertheless, secondary interests are not considered to be negative *per se*, and the problem does not lie in whether these interests can be defined as good or bad; rather, the problem is that damage occurs when secondary interests overlap and improperly influence, distort, or corrupt the professional's judgment with regard to the patient's health, the clinical trial, or education (28).

Another point of interest in our study was the dissatisfaction expressed by nine individuals (11.2%) with regard to continuing participation in the clinical trial that was not expressed to the researcher during the course of the study. It is possible that these omissions occurred due to an asymmetry in the relationship between the researchers and subjects, which is largely analogous to a doctor-patient relationship. The doctor figure usually reflects an image of power and knowledge; thus, questioning his/her judgement may not facilitate the researcher-subject relationship (29).

The results of the present study also demonstrate that even after patients read and discuss the consent form, which is written in lay language, with the investigator, it may be important to recheck during the follow-up which participants may have had the intention to abandon the trial but feared to spontaneously express such an opinion, or even to identify those individuals who did not understand the consent form or the trial. We were not able to analyze the consent forms from the trials we elected to evaluate, but all of them were written according to the guideline approved by our institutional ethics committee. The main reasons leading the participants to consider withdrawing from the clinical trials were the perception of risk in undergoing the tests required by the trial (Group I) and the frequency of required medical appointments (Group II). These findings indicate that many patients signed the consent form and agreed to participate in the study without actually understanding what was being asked of them. In these circumstances, studies evoke ethical issues, lead to great researcher responsibility and may cause personal risks to research subjects (30), as we have already seen (31).

Additionally, it was found that most of the participants did not withdraw from the study due to fear of discontinuation of their treatment at the hospital. This finding is in stark contrast to the principle of autonomy and leads us to reflect on how free the participants in clinical trials in developing countries really are to decide about remaining as a participant in such trials when they depend on the care provided by a public institution.

Potential study limitations

Our sample size may have been too small to achieve accurate information regarding our question of interest. Nevertheless, we think the study provides important information.

In addition, this investigation, as a retrospective study, is influenced by recall bias, even though recall ability was one of the criteria used for participant exclusion. It is also possible for a prospective study to present divergent findings.

The use of other interviewing techniques, and qualitative techniques in particular, could certainly contribute to the exploration of all of these concerns. Such techniques should be employed in future studies addressing these issues.

CONCLUSION

The results of the present study indicated that the main motivation for participating in a cardiology clinical trial was the personal benefit expected by the participants in both groups.

Although many of the patients confirmed their wish to withdraw from the trial, their dependence on the care provided by this medical center forced them to remain as subjects in the study.

Additionally, the relative lack of understanding of the study by some of the participants was evident, indicating that the use of an informed consent form in developing countries is a complex process that needs to be reviewed by institutions participating in multi-center clinical trials.

AUTHOR CONTRIBUTIONS

Meneguin S and Cesar LA planned and developed this study, developed the questionnaire, performed the statistical analyses, and wrote the manuscript. Meneguin S performed the administration of both the questionnaire and consent form.

REFERENCES

1. Macklin R. Bioethics, vulnerability and protection. Bioethics. 2003;17(5-6):472-86, http://dx.doi.org/10.1111/1467-8519.00362.
2. Zoboli ELCP. Vulnerability in biomedical research: a framework for analysis. In: Häyry M, Takala T, Herissone-Kelly P. Ethics in biomedical research. Netherlands: Rodopi BV; 2007.p.167-79.
3. Ministério da Saúde (Brasil). Conselho Nacional de Saúde. Resolução Nº. 196, de 10 de outubro de 1996. Available from: Accessed 2011 Oct 22.
4. Brody BA, McCullough LB, Sharp RR. Consensus and controversy in clinical research ethics. JAMA. 2005;294(11):1411-4, http://dx.doi.org/10.1001/jama.294.11.1411.
5. Ellenberg SS. Informed consent: protection or obstacle? Some emerging issues. Control Clin Trials. 1997;18(6):628-36, http://dx.doi.org/10.1016/S0197-2456(96)00130-4.
6. Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. N Engl J Med. 2001;345(2):139-42, http://dx.doi.org/10.1056/NEJM200107123450212.
7. Sample DA, Sinicrope OS, Wargovich MJ, Sinicrope FA. Post study aspirin intake and factors motivating participation in a colorectal cancer chemoprevention trial. Cancer Epidemiol Biomakers Prev. 2002;11(3):281-5.
8. Canvin K, Jacoby A. Duty, desire or indifference? A qualitative study of patient decision about recruitment to an epilepsy treatment trial. Trials. 2006;7:32, http://dx.doi.org/10.1186/1745-6215-7-32.
9. Shuhatovich OM, Sharman MP, Mirabal YN, Earle NR, Follen M, Basen-Engquist K. Participant recruitment and motivation for participation in optical technology for cervical cancer screening research trials. Gynecol Oncol. 2005;99(3 Suppl 1):S226-31, http://dx.doi.org/10.1016/j.ygyno.2005.07.093.
10. Ellis PM. Attitudes towards and participation in randomized clinical trials in oncology: a review of the literature. Ann Oncol. 2000;11(8):939-45, http://dx.doi.org/10.1023/A:1008342222205.
11. Yuval R, Halon DA, Lewis BS. Patients' point of view in heart failure trials. JAMA. 2001;285(7):883-84, http://dx.doi.org/10.1001/jama.285.7.883-b.
12. Yuval R, Uziel K, Gordon N, Merdler A, Khader N, Karkabi B, et al. Perceived benefit after participating in positive or negative/neutral heart failure trials: the patients' perspectives. Eur J of Heart Fail. 2001;3(2):217-23, http://dx.doi.org/10.1016/S1388-9842(00)00151-3.
13. Rienzo M, Kerr Saraiva JF, Nogueira PR, Gomes EPSG, Moretti MA, Ferreira JFM, et al. Combinação de amlodipino e enalapril em pacientes hipertensos com doença coronariana. Arq Bras Cardiol. 2009;92(3):173-9:177-83.
14. Machado César LA, Mathias Jr W, Armaganijan D, Gimenez V, Jallad S, del Monaco MI, et al. Trimetazidine to reverse ischemia in patients with class I or II angina: A randomized, double-blind, placebo-controlled dobutamine-atropine stress echocardiography study. Coron Artery Dis. 2007;18(4):259–63, http://dx.doi.org/10.1097/MCA.0b013e3280d5a7d0.
15. Oigman W, Plavnik FL, Almeida FA, Abuhab A, Stolt P, Glogflus S. Estudo nacional, multicêntrico, aberto, randomizado e comparativo para avaliar a eficácia e tolerabilidade da combinação de valsartana e amlodipino versus amlodipino isoladamente no tratamento da hipertensão arterial leve a moderada. Rev Bras Hipertens. 2007;14(3):148-56.
16. Bardin L. Análise de conteúdo. Lisboa: Edições 70; 2006.p.95-116.
17. Glancszpigel D. Clinical trial in Latin America. Appl. Clin. Trials [on line periodical]. 2003 [cited 2011 Oct 22]. Available from: http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Global+Trials/Clinical-Trialsin-Latin-America/ArticleStandard/Article/detail/80235
18. Marshall PA, Adebamowo CA, Adeyemo AA, Ogundiran TO, Vekich M, Strenski T, et al. Voluntary participation and informed consent to international genetic research. Am J Public Health. 2006;96(11):1989-95, http://dx.doi.org/10.2105/AJPH.2005.076232.
19. Yuval R, Halon DA, Merdler A, Khader N, Karkabi B, Uziel K, et al. Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction. Arch Intern Med. 2000;160(8):1142-6, http://dx.doi.org/10.1001/archinte.160.8.1142.
20. Ruffin MT, Baron J. Recruiting subjects in cancer prevention and control studies. J Cell Biochem. 2000;34:80-3, http://dx.doi.org/10.1002/(SICI)1097-4644(2000)77:34+<80::AID-JCB14>3.0.CO;2-E.
21. Sreenivasan G. Does informed consent to research require comprehension? Lancet. 2003;362(9400):2016-8, http://dx.doi.org/10.1016/S0140-6736(03)15025-8.
22. Cohn E, Larson E. Improving participant comprehension in the informed consent process. J Nurs Scholarsh. 2007;39(3):273-80, http://dx.doi.org/10.1111/j.1547-5069.2007.00180.x.
23. Henderson GE, Easter MM, Zimmer C, King NMP, Davis AM, Rothschild BB, et al. Therapeutic misconception in the early phase of gene transfer trials. Soc Sci Med. 2006;62(1):239-53, http://dx.doi.org/10.1016/j.socscimed.2005.05.022.
24. Grant JB, Mackinnon AJ, Christensen H, Walker J. CJ Med Ethics. 2009:35(12):768-73.
25. Burguess LJ, Sulzer NU, Hoosain F, Leverton L, Bliganut S, Emanuel S. Patients' motivations for participating in cardiovascular clinical trials: a local perspective. Cardiovasc J Afr. 2009;20(4):220-3.
26. Osuch JR. The power of the doctor, the vulnerability of the patient, and informed consent. Surg Neurol. 2004;61(5):494-6, http://dx.doi.org/10.1016/S0090-3019(03)00513-5.
27. Fletcher RH, Fletcher SW. Epidemiologia clínica: elementos essenciais. Porto Alegre: Artmed; 2006. v.8, p.154-78.
28. Thompson DF. Understanding financial conflicts of interest. N Engl J Med. 1993;329(8):573-6, http://dx.doi.org/10.1056/NEJM199308193290812.
29. Lings P, Seamark D, Seamark C, Sweeney K, Dixon M, Gray DP. The doctor-patient relationship in US primary care. J R Soc Med. 2003;96(4):180-4, http://dx.doi.org/10.1258/jrsm.96.4.180.
30. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. N Engl J Med. 2003;348(8):721-6, http://dx.doi.org/10.1056/NEJMsa021212.
31. Meneguin S, Zoboli ELC, Domingues RZL, Nobre M, César LA. Informed consent as viewed by patients participating in cardiology drug trial. Arq Bras Cardiol. 2010;94(1):4-9, http://dx.doi.org/10.1590/S0066-782X2010000100003.