Original Article

Informed Consent in the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Trial: A Survey of Collaborating Physicians

Tsuguya FUKUI[1)], Mahbubur RAHMAN[1)], Satoshi MORITA[2)], and Junichi SAKAMOTO[2)]

An anonymous postal survey was conducted among the physicians collaborating in a randomized controlled trial to examine their method of convincing patients, their consent process, the factors related to higher accrual, and the predictors of 100% success in the process of obtaining informed consent (IC). A total of 512 questionnaires were sent out and 448 responses were received, for a response rate of 87.5%. The 448 physicians solicited a total of 5,371 eligible patients (12.0 per physician), among which 3,763 patients (8.4 per physician) agreed to participate. One-fifth (22.3%) of the physicians were able to obtain IC from 100% of the patients they solicited. Physicians who thought that the information on the IC sheet was sufficient to obtain consent (odds ratio [OR]=2.0, 95% confidence interval [CI]=1.1–3.9; *p*=0.03) and those who did not consider that the patient's decision was influenced by relatives and friends (OR=0.2, CI=0.1–0.4; *p*=0.001), were significantly more likely to obtain IC from 100% of the eligible patients. Three-fourths (73.2%) of the physicians targeted only patients who they perceived would easily provide IC, and 81.2% favored some form of incentives for patients. The results of this study should be useful for efficiently implementing randomized controlled trials in Japan. (*Hypertens Res* 2006; 29: 471–474)

***Key Words*: informed consent, randomized controlled trial, collaborating physicians, patient recruitment, Candesartan Antihypertensive Survival Evaluation in Japan**

Introduction

Informed consent (IC) is prerequisite for any medical clinical research. However, it is a cumbersome task from the viewpoint of the investigator (*1*). Both obtaining and giving IC are very complex processes, and especially so in randomized controlled trials (RCTs). Translating into laymen's language the scientific merits of the trial, the risks and benefits of the research, the randomization procedures, and various other complexities is a challenging task for investigators. Moreover, it has been shown that clinical treatments are more likely to succeed if patients understand the information disclosed to them (*2*). Many factors in regard to the patients, such as older age, level of education, impaired cognitive functions, and locus of control, determine the quality of IC (*3*). In terms of the investigators, such factors as communication skills and their resulting doctor-patient relationship might also play an important role in determining the quality of IC.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) is a prospective, multicenter, open-label, randomized controlled trial to compare the effectiveness of an

From the [1)]Clinical Practice Evaluation and Research Center, St. Luke's Life Science Institute, St. Luke's International Hospital, Tokyo, Japan; and [2)]Department of Epidemiological and Clinical Research Information Management, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Address for Reprints: Tsuguya Fukui, M.D., Ph.D., Clinical Practice Evaluation and Research Center, St. Luke's Life Science Institute, St. Luke's International Hospital, 10–1 Akashi-cho, Chuo-ku, Tokyo 104–8560, Japan. E-mail: fkts@luke.or.jp

Received January 28, 2005; Accepted in revised form March 30, 2005.

Table 1. Physicians' Experience and Views Regarding Consenting Process

Statement	Physicians' response (%)*		
	Agree**	Neutral	Disagree**
1. The information on the "Information and Consent" form provided from the CASE-J management was sufficient to get consent from the patients	71.3	14.9	13.8
2. I emphasized the positive aspects (especially for the patients' benefit) of participating in the CASE-J Research Study during my explanation to patients	55.6	32.7	10.7
3. I only targeted the patients who would agree for participation	73.2	17.7	9.1
4. I had a difficult time to explain "randomized controlled protocol" to the patients	46.5	31.4	22.1
5. It was my concern that it would affect the "doctor-patient relationship" by asking patient participation for the clinical trial	32.6	22.8	44.6
6. The procedure to complete the informed consent was cumbersome	45.8	27.3	26.9
7. To get a positive response, some incentives for the participants may be helpful, so that should be considered	81.2	11.3	7.5
8. The decision-making for patients was influenced by family member(s) or friend(s)	40.6	23.7	35.8
9. It was easier to obtain consent from patients whose risk factors and severity of disease were greater	16.7	50.0	33.2

*Denominators for each of the categories were based on the total number of data available for that category. **"Strongly agree" and "agree," "strongly disagree" and "disagree" were combined into "agree" and "disagree," respectively.

angiotensin II receptor antagonist (candesartan cilexetil) and a calcium channel blocker (amlodipine besilate) in reducing the incidence of cardiovascular events in high-risk hypertensive patients (*4*). Enrollment began in September 2001 and follow-up is to be completed in December 2005. Written IC was taken before the patient was enrolled after explaining the following items: the objectives of the study, the duration of treatment, the random nature of the treatment allocation, the availability of alternative drugs, the possible adverse reactions of the treatment, the voluntary nature of participation, the fact that patients refusing to participate will not be disadvantaged in any way, the freedom to withdraw from the study at any time, the protective measures taken to ensure privacy, and the approval of the CASE-J trial by a university ethics committee (*4*).

The objectives of the present study were to examine the factors related to investigators' higher success rate in obtaining IC, their perspectives on the IC procedure, and the main causes of patients' refusal to participate as perceived by the investigators.

Methods

We sent questionnaires to 512 collaborating physicians, requesting information on demographics, academic background, and IC in the CASE-J trial.

The Questionnaire

The questionnaire contained 12 questions related to IC. Nine questions were answered on a five-point scale (strongly agree, agree, neutral, disagree, and strongly disagree). Questions covered the number of patients solicited by the collaborators, the number of patients who finally agreed to participate, and the reasons for refusal to participate as perceived by the investigators.

Procedure

The study was conducted in January 2003. We sent a questionnaire with a pre-paid, pre-addressed envelope to facilitate the return of the completed questionnaire to all the collaborating physicians of the CASE-J trial. A month after the initial postal mail, a written reminder with an additional questionnaire was sent to the non-responding physicians.

Statistical Analyses

Statistical analyses were made with STATA statistical software (*5*). All the statistical tests were two-tailed and p values of <0.05 were considered statistically significant. To elicit factors responsible for success in obtaining IC, a logistic regression analysis was performed, with 100% success in obtaining IC from the patients taken as the dependent variable, and age, sex, specialty, working place, history of taking clinical study courses at medical school, history of participa-

tion in other clinical trials/studies, contemporary participation in another trial/study, attitudes and perceptions about IC procedures, and number of patients solicited taken as independent variables. In addition, univariate analyses were performed on collaborating physicians' attitudes and perceptions about IC. A multiple regression model was also employed, with the percentage of success in IC taken as the dependent variable and the above-mentioned variables considered as independent variables.

Results

Of the 512 questionnaires sent to the collaborating physicians, responses were received from 448 investigators, which represented a response rate of 87.7%. Details of the demographic characteristics of the respondents, and a study about their attitudes toward and reasons for participating in the CASE-J trial based on results from the same survey have been published elsewhere (*6*, *7*).

Physicians' Experience and Views on the Consent Process

In total, 448 physicians solicited 5,371 eligible patients (12.0 per physician), 1,608 patients declined (3.6 per physician), and 3,763 patients (8.4 per physician) agreed to participate. One-fifth of the physicians (22.3%) were able to obtain IC from 100% of the patients they solicited. Table 1 shows the physicians' attitudes and perceptions about the IC process in the CASE-J trial. The majority of the physicians thought that the information on the IC sheet was sufficient (71.3%), emphasized the positive aspects of the trial to their patients (55.6%), targeted only patients who they thought were likely to give IC (73.2%), and favored use of an incentive for patients (81.2%).

Predictors of Higher Success Rate in Obtaining IC

Logistic regression analyses revealed that collaborating physicians who thought that the information on the IC sheet was sufficient to obtain IC (odds ratio [OR]=2.0, 95% confidence intervals [CI]=1.1–3.9; $p=0.03$), and those who did not consider that the patient's decision was influenced by relatives and friends (OR=0.2, 95% CI=0.1–0.4; $p=0.001$) (Table 2), were significantly more likely to obtain IC from 100% of the patients solicited. The greater the number of patients solicited, the lower was the likelihood of obtaining IC from 100% of patients ($p=0.01$). In addition, physicians involved in another clinical study/trial were less likely to accrue IC from 100% of the patients (OR=0.6, 95% CI=0.3–1.1; $p=0.08$). In a multiple regression model in which the percentage of success in obtaining IC was considered a dependent variable, similar predictors were found to be significant, although the number of patients solicited was not a significant predictor in this model. However, the pseudo r^2 value (0.175) in the logistic model was higher than the adjusted r^2 value (0.135) in the multiple regression model.

Table 2. Multivariate Logistic Regression Models to Identify Predictive Factors of Physician in Obtaining IC from 100% of the Patients Solicited

Predictors	OR (95% CI)
Age	
<51 years	1.0
≥51 years	0.7 (0.4–1.3)
Sex	
Male	1.0
Female	2.6 (0.7–9.0)
Clinical studies/epidemiology courses at medical school	
No	1.0
Yes	1.7 (0.8–3.7)
History of participation into clinical trials	
No	1.0
Yes	0.9 (0.5–1.8)
Contemporary participating into another trial	
No	1.0
Yes	0.6 (0.3–1.1)
Physician who thought that information on IC sheet was enough to obtain consent	
No	1.0
Yes	2.0 (1.1–3.9)
Physician who consider that the patient decision was influenced by family members/friends	
No	1.0
Yes	0.2 (0.1–0.4)
Number of patients solicited	0.95 (0.92–0.99)

IC, informed consent; OR, odds ratio; CI, confidence interval. Model details: pseudo $r^2=0.175$.

Discussion

Our previous analysis showed that 29.9% (1,608/5,371) of patients refused to participate in the CASE-J trial for the following reasons: fear of being a subject of research (35.9% of patients), opposition from family member (26.7%), unwillingness to change the medicine already prescribed (24.5%), and inability to understand the significance of the trial (11.8%) (unpublished observations). This means that 73.3% of the patients who refused to participate (*i.e.*, all those who refused for reasons other than the opposition of family members) might have been convinced to participate through some effort on the part of their physicians. The characteristics of the collaborating physicians who were successful in obtaining IC from 100% of the patients they approached were as follows: they thought the information provided on the IC sheet was

sufficient to obtain IC, and they assumed that the participation of patients was not influenced by their family members or friends. The physicians who considered that the information on the IC sheet was sufficient to convince patients seemed to be confident enough in themselves and thus to care little about the formal information on the sheet. The physicians who were unable to convince some or many of their patients may have preferred to focus on the patients autonomy, granting due consideration to the thoughts and emotions of the patients, who in turn took this opportunity to express their true feelings. Given this complex interplay, it is overly simplistic to suppose that the obtaining of IC is entirely dependent on the investigators. Actually IC is not an event but a process, which is dependent on both the investigators and subjects (*8*), although the role of the former is more important.

Obtaining consent to participate in research is not always straightforward. How much information should be disclosed to the patients remains subject to debate, since a substantial proportion of patients do not want full disclosure, but prefer a paternalistic model in which their physician makes decisions for them. In our study we found that 73.2% of the collaborating physicians targeted particular patients who would likely to participate in the CASE-J trial, which means that those subjects were likely to favor the paternalistic model. Thus information disclosure could be in accordance with the type of view the patients have regarding the decision-making process. Irrespective of patients' preferences, however, they should get all possible information on the medical/surgical/research procedures.

There are some limitations to this study. First, most of the respondents were male (94.6%), which is not representative of the gender distribution of Japanese physicians (85.7% of Japanese physicians were male in 2000) (*9*). Second, the physicians surveyed in this study were mostly cardiologists and generalists (79.8% of total) (*6*), whereas these specialties collectively constituted only 30.6% (*10*) of the total physician population in Japan. Thus, the findings here could be biased because of a way of thinking unique to cardiology and general medicine. Third, the IC procedure for trials in different clinical fields in different societies could vary because of unique clinical, social and bioethical characteristics, which would lead to different participation rates. Fourth, we did not include any questions regarding the quality of the IC process. Despite these limitations, the results of this study could be useful for physicians/clinical researchers in general and for cardiologists/generalists in particular. Since the study is based on a hypertension evaluation trial, physicians interested in participating in future trials of this kind might also benefit from the present results.

The following measures would be useful to attain a higher success rate in obtaining IC. First, collaborating physicians should at least attend educational sessions on clinical research methodologies including IC and communication skill. Second, medical students should receive training in IC and its legal aspects. IC is not only important for conducting clinical research but also for medical/surgical procedures. Thus its inclusion as part of the curriculum for medical students would raise the overall standard of patient care as well as clinical research. Third, information given on the IC sheet should include possible benefits and risks of interventions. The sheet must be written in plain language that is understandable to a wide range of patients with different educational levels.

The results reported here have important implications regarding collaborating physicians' attitudes towards IC and factors related to a high success rate in obtaining IC.

Acknowledgements

The authors wish to thank all the collaborating physicians who participated in the survey.

References

1. Verheggen FW, van Wijmen FC: Myth and reality of informed consent in clinical trials. *Med Law* 1997; **16**: 53–69.
2. Lavori PW, Sugarman J, Hays MT, Feussner JR: Improving informed consent in clinical trials: a duty to experiment. *Control Clin Trials* 1999; **20**: 187–193.
3. Lavelle-Jones C, Byrne DJ, Rice P, Cuschieri A: Factors affecting quality of informed consent. *BMJ* 1993; **306**: 885–890.
4. Fukui T, Rahman M, Hayashi K, *et al*: Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients. Rationale, design and methods. *Hypertens Res* 2003; **26**: 979–990.
5. STATA Corporation: STATA Statistical Software Version 7.0 (Intercooled). College Station, STATA Corporation.
6. Rahman M, Morita S, Fukui T, Sakamoto J: Physicians' choice in using internet and fax for patient recruitment and follow up in a randomized controlled trial. *Methods Inform Med* 2004; **43**: 288–292.
7. Rahman M, Morita S, Fukui T, Sakamoto J: Physicians' attitude towards and reasons for participation in the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. *J Epidemiol* 2005; **15**: 38–40.
8. Feld AD: Informed consent: not just for procedures anymore. *Am J Gastroenterol* 2004; **99**: 977–980.
9. Anonymous: Survey on physicians, dentists, and pharmacist. *J Health Welfare Stat* 2002; **9**: 472 (in Japanese).
10. Anonymous: Health care manpower. *J Health Welfare Stat* 2002; **9**: 170–183 (in Japanese).