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Recruitment of Patients for a Clinical Trial: Factors on the Physician Side and Reasons on the Patient Side

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Abstract

Objectives To examine the factors related to actual patient recruiters among the physicians who initially agreed to collaborate in a randomized control trial.

Methods We conducted a questionnaire survey of 679 physicians (512 actual recruiter and 167 non-recruiters) who had initially agreed to recruit patients for a clinical trial to determine factors to predict who would actually do so.

Results Response rates among recruiters and non-recruiters were 87.5% and 73.1%, respectively. Multivariate logistic regression model showed that the proportions of regular users of computer [odds ratio (OR) =2.1, 95% confidence intervals (CI)=1.3-3.3] (p=0.002) and current participants in other clinical trials (OR=2.2, CI=1.5-3.4) (p=0.001) were significantly higher among recruiters than non-recruiters. Patients' reasons for non-participation as perceived by the physicians did not differ between recruiters and non-recruiters.

Conclusion Results of this study might be useful in predicting actual recruiters at the outset of clinical trials.

Key words: physician participation, randomized controlled trial, patient recruitment, Japan

Introduction

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial is a prospective, multicenter, open-label, randomized controlled trial in high-risk hypertensive patients to compare the incidence of cardiovascular events between those assigned to an angiotensin II receptor antagonist (candesartan cilexetil) and those to a calcium channel blocker (amlodipine besilate) (1). This trial is unique in that its data collection and management are done either by a sophisticated Web-based system or by fax. If the system is substantiated to be usable, effective, and economically feasible, a Web-based system of this kind will become widespread for large scale, multicenter clinical trial in the near future (1). Even if a sophisticated computer system is available, patient recruitment by a physician is the sine qua non first step in a clinical trial.

Successful recruitment of patients for a clinical trial depends on many factors, including the number of patients collaborating physicians see, complexity/simplicity of inclusion/exclusion criteria and the process of obtaining informed consent, and their enthusiasm for contributing to the success of the trial among others. In a recent systematic review by Ross et al, many factors were identified as barriers for a clinical trial from physicians' perspectives, including time constraints, lack of staff, worry about the impact on doctor-patient relationship, concern for patients, loss of professional autonomy, difficulty with the consent procedure, lack of proper incentives, and uninteresting research questions (2). Thus, it is natural to expect that not all physicians who initially agreed to collaborate actually recruit patients for a clinical trial. It would be helpful for investigators to predict at the outset of a clinical trial who would actually recruit

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patients.

This study was designed to determine the factors related to actual recruiters among the physicians who had initially agreed to collaborate in recruiting patients for the CASE-J trial.

Methods

We sent questionnaires to all 679 physicians who had initially agreed to collaborate in recruiting patients for the CASE-J trial in January 2003 immediately after the end of patient enrollment.

The questionnaire

The questionnaire was comprised of questions related to demographics, academic background, prior experience in another clinical trial/study, current participation in another clinical trial, willingness to participate in future trials, and computer use on a regular basis. Several additional questions were included for actual recruiters: number of patients they actually solicited for participation, the number of patients who finally agreed to participate, and the physicians' accounts of patients' refusal to participate. For the last item physicians were asked to quantify the number of patients who refused to participate based on the set of reasons.

Procedure

Among 679 physicians who had initially agreed to collaborate, 512 actually recruited patients and 167 did not. We asked them to answer questionnaire anonymously with a pre-paid, pre-addressed envelope to facilitate the return of the completed questionnaire. One month after the initial postal mail, a reminder with an additional questionnaire was sent to the non-responding physicians.

Statistical analyses

Statistical analyses were made with STATA statistical software (3). All the statistical tests were two-tailed and P values of <0.05 were considered as statistically significant. To determine factors predictive of actual recruiters, a logistic regression analysis was performed taking into consideration actual recruiters of patients as a dependent variable, and age, sex, speciality of practice, working place, prior experience in other clinical trial/study, current participation in other clinical trial, and computer use on a regular basis as independent variables. Bivariate logistic regression procedures were performed first, and significance at the level of p=0.2 was considered as an entry criterion for multivariate logistic model. Chi-square test was performed for categorical data while either Student's t-test or Mann-Whitney test was performed for continuous data to compare characteristics between recruiters and non-recruiters.

Table 1. **Characteristics of Subject Physicians**

Characteristics of Subject Physicians	Recruiters (n=448)	Non-recruiters (n=122)	P value
Mean age (range)	49.3 (28-77)	49.0 (27-77)	0.71
Sex			
- Male (%)	94.4	94.3	0.96
- Female (%)	5.6	5.7	
Mean number of years after graduation (range)	25.4	24.9	0.68
Speciality of collaborating physicians			0.79
- Cardiology	42.4	40.5	
- Internal medicine	37.1	40.5	
- Others	20.5	19.0	
Working site (%)			
- University hospital (%)	9.3	5.8	0.25
- Other National/Public hospital (%)	3.6	2.5	0.42
- Private hospital (%)	25.6	19.8	0.06
- Own private clinic (%)	61.5	75.2	0.02
Prior experience of participating in clinical trial/study	76.5	81.2	0.28
Current participation in other trial/study	67.4	47.9	0.001
Interested in participating in a clinical trial in the future	68.8	66.1	0.001
Regular users of computer	82.9	70.5	0.01
Mean number of patients solicited	12.0	-	
Mean number of patients who agreed to participate	8.4	-	
Mean number of patients who declined to participate	3.6	-	

Denominators for each of the categories were based on the total number of data available for that category

Results

Response rate

Of questionnaires sent to 679 physicians, responses were received from 448 (87.7%) out of 512 recruiters and 122 (73.1%) out of 167 non-recruiters, providing an overall response rate of 83.9%.

Main characteristics- actual recruiters vs non-recruiters

Characteristics of the respondents are shown in Table 1. The actual recruiters were more likely to be working in a private hospital (p=0.06), a current collaborator of another clinical trial (p=0.001), willing to participate in a future trial (p=0.001), and a regular computer user (p=0.01). On the other hand, non-recruiters were more likely to be private practitioners (p=0.02). Other characteristics were not significantly different between recruiters and non-recruiters.

The number of patients solicited

Recruiters solicited more patients for participation than non-recruiters (12.0 patients per physician vs 4.7 patients per physician, p=0.001). A total of 5,371 eligible patients were solicited to enroll by 448 actual recruiter physicians and 3,763 (8.4 patients per physician) of them were enrolled. On the other hand, 271 eligible patients were approached by 58 non-recruiter physicians (47.5% of 122 respondents), and none of them agreed to participate. The remaining 64 non-recruiter physicians did not solicit any patient to begin with.

Table 2. **Patients' Reasons for Refusal to Participate as Perceived by Physicians**

Category	Number of patient refused	
	Recruiters	Non-recruiters
Fear of being a subject of a study	578 (35.9))	125 (46.1)
Opposition from family members	430 (26.7)	35 (12.9)
Unwillingness to change therapy	394 (24.5)	63 (23.2)
Did not understand the significance of the trial	190 (11.8)	37 (13.7)
Others	16 (1.0)	11 (4.1)

* Physicians were asked to categorize the number of patients refused to participate, and after that, they were summed up and tabulated.

Predictors of actual recruiters for the CASE-J trial

Logistic regression analysis revealed that the physicians who were regular users of computer [odds ratio (OR) =2.1, 95% confidence intervals (CI)=1.3-3.3] (p=0.002) and current participants in other clinical trials (OR=2.2, CI=1.5-3.4) (p=0.001) were more likely to actually recruit patients for the CASE-J trial.

Patients' reasons of refusal to participate

Actual recruiter physicians thought that patients' 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%) seemed to be the main reasons behind the refusal by patients (Table 2). On the other hand, the corresponding figures for non-recruiter physicians were 46.1%, 12.9%, 23.2%, and 13.7%, respectively. Thus, the proportion of patients who refused to enroll due to the scare of being a subject of research based on physician observation was higher for non-recruiters than that of recruiters (p=0.001) while the reverse was true for opposition from family members (p=0.001).

Discussion

In spite of their initial intention, about one-fourth (24.6%) of the physicians (169/679) did not recruit patients for the CASE-J trial. Regular computer users were more likely to actually recruit patients. This could be due to the feature of the CASE-J trial that patients' enrollment, follow-up and other communication with data management center are possible through sophisticated Web-based system, in addition to fax. Thus, physicians who were not comfortable operating Web-based system, might have felt a resistance to collaborate. Current participation in other clinical trial turned out to be a significant factor associated with actual patient recruitment. This means that the recruiters are more familiar with and enthusiastic about clinical trials than non-recruiters.

Among the patients who refused to enroll, nearly one-third (35.9%) for recruiter and half (45.1%) for non-recruiter were afraid of being a subject of the research. A sizeable number also mentioned about the opposition from family members and unwillingness to change therapy. The reasons behind the above-mentioned behaviors of the patients and their family members could be manifold. Patients might have serious health problems to think about participating into a clinical study to provide scientific data for other patients in the future. On the other hand, physician factor might have a link with this situation too. Many of the physicians could not obtain informed consent because they did not explain whole scenario of informed consent to the patients properly.

Based on the current data, patient recruitment for a clinical trial can be improved by the following measures. First of all, instruction in detail and support on daily basis in operating computer program should be provided to the potential collaborating physician, so that they can improve their computer skills to expedite enrollment and follow-up procedure as we recommended in our previous study (4). However, this strategy is suitable for only Web-based clinical trials. Second, formal training on how to obtain informed consent may overcome the problems, which may arise by inexperienced approach to soliciting informed consent. Third, the appeal to potential collaborating physicians on the value of clinical trials should be repeated at explanatory meetings as frequently as possible.

There are some limitations to this study in terms of generalizability in particular. First, most of the respondents were male physicians (94.4%), not representative of gender distribution of Japanese physicians (85.7% were male in 2000) (5). Second, physicians surveyed in this study were mostly cardiologists and internists (79.8% of the total) whereas these specialties collectively constituted only 30.6% of the total physician population in Japan (6). Third, the factors "regular computer user" is only generalizable for Web-based clinical trials. Thus, they neither represent the entire physician community in terms of specialty and the topic of the clinical trial conducted in Japan. Further studies must include investigators in other specialty fields.

The results reported here have important implications regarding the factors associated with successful recruitment of patients in clinical trials. Appropriate steps should be taken in the planning stage to efficiently recruit patients for a clinical trial.

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