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Clinical trials for drug approval : a pilot study of the view of doctors at Tokushima University Hospital

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Abstract : The development of new and useful pharmaceutical drugs is essential in order to improve the quality of drug therapeutics. Clinical trials play a central role in drug development. Over time, the clinical trial infrastructure has improved and is now integrating the contribution of clinical research coordinators (CRC). Nevertheless, the attitude of doctors towards clinical trials still favors conventional/historical methodologies. In the present study, we explored the view of doctors towards clinical trials for drug development, in order to improve communication among participants, sponsors, and investigators. A questionnaire was designed for this pilot study. The questionnaire included general attitudes, difficult points, the benefit of doctors in participating as investigators, special attention requirements, and the expected role of CRC in clinical trials for drug approval. In addition, the appropriate use of the outpatient clinic was examined. The questionnaire was provided to doctors in each department of Tokushima University Hospital in 2000 and 2004. Because of the small number of subjects included in this pilot study, no statistical analysis is presented.

A total of 89 (81%) and 62 (56%) doctors among 110 responded to the survey in 2000 and 2004, respectively. Inquiries about the familiarity of the physicians with clinical trials for drug approval revealed that 84% in 2000 and 66% in 2004 were aware of such trials. The attitude towards participating as investigators in the clinical trials was favorable, with a response of 66% in 2000 and 58% in 2004. Patients' refusal and the informed consent process were considered difficult areas by many doctors. Expected roles of CRC included activities based on the nurse's specialty. Although many doctors agreed to take care of the study participants separately from the clinical practice, they lacked the time to do so.

In spite of the doctors' workload reduction by introduction of the CRC concept, their views regarding clinical trials for drug approval remain conventional. Further refinement in the support process by CRC should be considered in our hospital, and the views of the doctors should be investigated in a larger study, in order to promote clinical trials for drug approval in Japan. J. Med. Invest. 53 : 292-296, August, 2006

Keywords **:** *doctors' view, clinical trials, questionnaire, drug approval*

Received for publication May 9, 2006 ; accepted June 8, 2006.

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INTRODUCTION

The development of new and useful pharmaceutical drugs is essential to improve the quality of drug therapeutics. Among the various processes of drug development, clinical trials play a central role. Clinical trials in Japan are associated with certain scientific, ethical, and regulatory problems (1). Compared to Japan's contributions in basic research, clinical research contributions were reported as still unsatisfactory in 2002 (2) ; thus, the promotion of clinical trials is an important issue in Japan. As for clinical trials for drug approval by regulatory agents, the infrastructure is still developing since the introduction of the Good Clinical Practice approved by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (3) in 1997. Contributions of coordinators to clinical trials, a common feature of clinical trials performed in the United States, is now popular in Japan. Training of clinical research coordinators (CRC) is emphasized in the plan for promotion of clinical trials for drug approval by the Ministry of Health, Labor and Welfare and the Ministry of Culture and Science of Japan.

In Tokushima University Hospital, an academic hospital in Shikoku district (710 beds and 160 medical doctors except residents), the Clinical Trial Center for Developmental Therapeutics was organized in 1999 as a supporting system for clinical trials. Four nurses, two pharmacists and one nutritionist work as CRC and coordinate the communication among participants, sponsors, and investigators (4). Currently, the new system for performing clinical trials for drug approval is being integrated as a standard method. Since a clear understanding of the attitude of doctors may contribute to the progress of clinical trials, the attitude of doctors towards clinical trials for drug approval was investigated using pilot questionnaires in 2000 and 2004. In the present paper, the results of these investigations are reported and discussed.

METHODS

A questionnaire was designed specifically for this pilot study. The questionnaire started by examining general attitudes towards clinical trials for drug approval on a four-point scale (strongly agree, agree, disagree, and strongly disagree). This was followed by practical questions, such as difficulties regarding participation as investigators, areas of special attention, and the expected role of CRC in clinical trials for drug approval. An open-ended question to describe the doctors' benefits of involvement in clinical trials for drug approval was also included. In addition, another question concerned the appropriate use of the outpatient clinic. Lastly, there was an opportunity to give more detailed responses if desired. The questionnaire was provided to each department of Tokushima University Hospital in 2000 and 2004, excluding the outpatient clinic question. In order to survey the attitude of possible principal investigators, about 5-10 staffs (non-residents) were mainly asked to respond in each department, since principal investigators in clinical trials for drug approval are restricted to staffs in Tokushima University Hospital. In view of the small number of subjects included in this pilot study, no statistical analysis of the data was performed. The results have been used to improve the activity of CRC in our hospital and to provide information for the development of future studies.

RESULTS

Characteristics of questioned doctors

A total of 89 (81%) and 62 (56%) doctors among 110 responded to the survey in 2000 and 2004, respectively. Among the questionnaires, 61 doctors (69%) in 2000 and 38 doctors (61%) in 2004 had contributed to clinical trials for drug approval after 1997, the year that the Good Clinical Practice was implemented in Japan.

General attitudes towards clinical trials for drug approval

When questioned regarding feelings about the clinical trials, 84% in 2000 and 66% in 2004 stated that they were familiar with clinical trials and the drug approval process, as shown in Figure 1A.

Regarding the attitude towards participating as investigators in the clinical trials, 66% in 2000 and 58% in 2004 gave favorable responses (Figure 1B). One doctor mentioned low confidence in clinical skills as a reason for hesitating to participate.

Difficult points of investigators participating in clinical trials for drug approval

Selected answers to this question are shown in

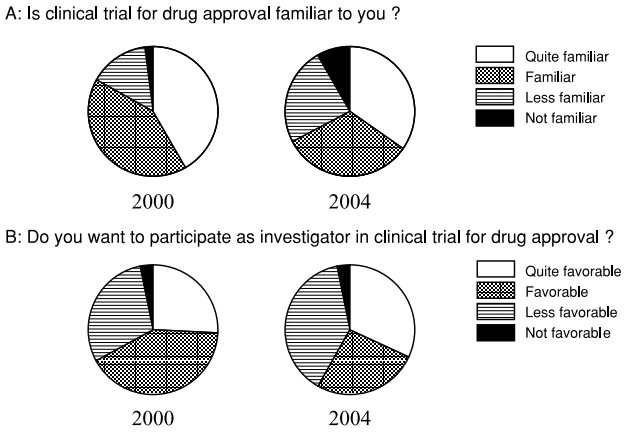

Figure 1 : General view of clinical trials for drug approval (Figure 1A), and the attitude towards participation as investigators in clinical trials for drug approval (Figure 1B).

Figure 2. In 2000, the difficulties were patients' refusal (77%), informed consent process (64%), cumbersome procedures (36%), and reporting of adverse events (26%). In 2004, the difficulties were similar, but with different frequencies : patients' refusal (47%), informed consent process (44%), cumbersome procedures (47%), and reporting of adverse events (44%).

Doctors' benefit of participating as investigators in clinical trials for drug approval

An open-ended question to describe the benefits of involvement of doctors in the clinical trials was added to the survey in 2004. Among 26 doctors who responded, the benefits were advancement of therapy (6), close contact with developmental drugs (8), therapeutic options (4), financial benefits for the hospital (6), and a chance to come into contact with clinical trial methodology (2).

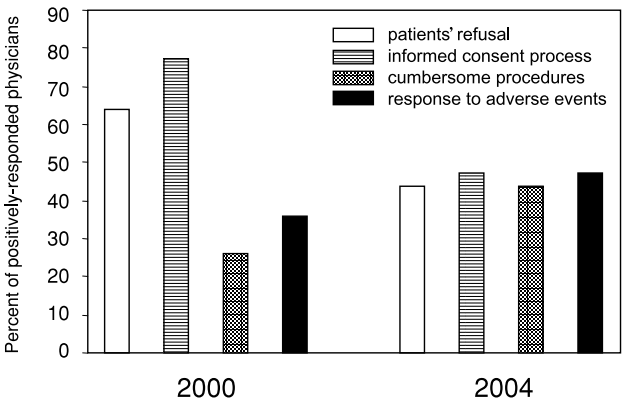

Figure 2 : Difficult points of participation of investigators in clinical trials for drug approval.

Areas that require special attention in clinical trials for drug approval

In 2000, special attention was devoted to patients' views (41%), patients' physical status (43%), view of the family (20%), doctor-patient relationship (82%), adverse events (75%), following protocol (48%), and participant numbers (48%). In 2004, special attention was devoted to patients' views (19%), patients' physical status (27%), view of the family (24%), doctor-patient relationship (63%), adverse events (69%), following protocol (27%), and participant numbers (29%).

Expected role of CRC in clinical trials for drug approval

Regarding the time of support by CRC, 83% and 84% of the responders wanted support throughout the entire period in 2000 and in 2004, respectively.

When asked about the expected roles of CRC, doctors selected the following answers. In 2000, doctors expected support from CRC in obtaining informed consent (62%), explanation of the medication schedule (53%), confirmation of the compliance (60%), monitoring of the patients' views (56%), follow-up of the physical status (55%), response to adverse events (55%), management in protocol observance (43%), schedule management (44%), making the case report forms (36%), response in monitoring and audit (44%), explaining the clinical trial itself (37%), and general consultation of the clinical trial itself (48%). In 2004, the doctors expected support from CRC in obtaining informed consent (77%), explanation of the medication schedule (81%), confirmation of compliance (48%), monitoring of patients' view (27%), follow-up of the physical status (37%), response to adverse events (48%), management in protocol observance (53%), schedule management (74%), making the case report forms (69%), response in monitoring and audit (44%), explanation of the clinical trial itself (37%), and general consultation of the clinical trial itself (50%).

Favorable use of special outpatient rooms for study participants

In clinical trials for outpatients in Japan, doctors generally care for study participants at the same clinic as ordinary patients. To provide good circumstances for study participants, our hospital has a special outpatient room for the participants. In 2004, the doctors were asked about using the special room. Forty-five (73%) agreed to care for study

participants separately from their clinical practice. Twenty-six (42%) agreed to set aside time for study participants separately from their ordinary patients, but only 62% of the agreeing physicians had sufficient time to perform this task.

DISCUSSION

In Japanese clinical trials, investigators once took a more active role than their counterparts in the United States (5). Investigators in Japan had to do virtually everything, from patient care to administrative work, during the course of the study (6). It is highly likely that the excessive workload borne by investigators in Japan had an adverse effect on the quality of the trials (7) and many doctors considered clinical trials, especially these for drug approval, an annoyance. Since introducing the concept of CRC, the workload reduction seems to have been achieved, if only partly, which is also the case at Tokushima University Hospital. Nevertheless, as shown in Figure 1, fewer doctors are familiar with clinical trials in 2004 than in 2000, and fewer feel favorable to participate as investigators in 2004 than in 2000. As shown in Figure 2, many doctors considered cumbersome procedures and reporting of adverse events problems in the pursuit of clinical trials. Since contributions of CRC can be expected in these fields, more refinement in the support process by CRC is necessary. Nevertheless, the widespread knowledge that clinical trials have an essentially complicated process may make clinical trials less familiar and more unfavorable.

There is evidently a strong resistance among the Japanese to be subjects in clinical trials. The reason for this resistance appears to be multifactorial. The lack of volunteer spirit and, more importantly, the lack of benefits from participation are reasons often mentioned (6). In addition, doctors tend to fear a negative response from patients when referral to the trial is proposed (8). As shown in Figure 2, many doctors found difficulty in the patients' refusal and informed consent process. As reported by Rahman *et al*. (9), training, a manual for obtaining informed consent and a face-to-face demonstration of patient registration and follow-up procedures for the potential participants could be a useful tool to overcome this problem.

Based on long-held principles of research ethics, the central societal purpose of trials is ideally the advancement of therapy for future patients (10). Nevertheless, in the mailed survey to oncology specialists of the United States, Joffe *et al*. (11) reported many respondents viewed the main societal purpose of clinical trials as benefiting the participants rather than creating general knowledge to advance future therapy. The patient's perception of personal benefit was the most important factor in the patient's decision (12). In the present study, numerous doctors considered clinical trials for drug approval as a therapeutic option.

In the United States, the duties of CRC are well defined (13). In Japan, CRC is still a new concept and nurses and pharmacists mainly play CRC roles in addition to their other expected roles. In Tokushima University Hospital, nurses mainly play the role of CRC on the basis of nurse specialty (14). Therefore, the expected roles of CRC include the activity based on the nurse's specialty. Further study is warranted to evaluate the appropriate duties of CRC in Japan.

As part of establishing the infrastructure for clinical trials, creation of an environment in which patients can easily participate would improve the quality of clinical trials, in addition to creating outpatient clinics exclusively for clinical trials (6). In Tokushima University Hospital, a special outpatient room was prepared for study participants, and it was used by many doctors. In 2004, the doctors were asked about the favorable use of the special room. Although many doctors agreed to care for the study participants separately from their clinical practice and 42% of this group wanted to set aside time for study participants separately from their ordinary patients, generating the time to do so was difficult.

In the present article, the view of the doctors toward clinical trials for drug approval at Tokushima University Hospital were reported. Because of significant limitations of this pilot study, the view of doctors should be expanded in a larger study, in order to promote clinical trials for drug approval in Japan. In these studies, the significance of background, such as specialty and types of past clinical trial experiences, on the view should be examined.

ACKNOWLEDGEMENTS

The authors would like to thank the doctors at Tokushima University Hospital who responded to the survey.

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