

Review

**The Present Status and Problems of Clinical Trials  
at The Jikei University Hospital :  
A Report by Clinical Research Coordinators**

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*ABSTRACT*

In the 3 years since the new Good Clinical Practice (GCP) guidelines for clinical trials came into effect, steady efforts have been made to improve and introduce innovations to the system of clinical trial management at The Jikei University Hospital. The Clinical Research Office was established to provide secretarial services, including clerical services for the Institutional Review Board and drawing up contracts for clinical trials, and to provide a liaison service by clinical research coordinators (CRCs) at sites of clinical research. As the role of CRCs in the hospital came to be understood more widely, requests for introductions of CRCs have increased. A system must be established under which CRCs are more readily introduced to improve the efficiency and reliability of clinical trials and thereby earn the confidence of sponsors. For this reason, more members of the hospital staff should deepen their understanding of what clinical trials and CRC mean and to cooperate to ensure future development of support system for clinical trials.

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**INTRODUCTION**

In the 3 years since the new Good Clinical Practice (GCP) guidelines for clinical trials came into effect, steady efforts have been made to improve and introduce innovations to the system of clinical trial management at The Jikei University Hospital. The Clinical Research Office was set up to establish this system for the harmonious conduct of clinical trials. This office has two major functions. The first is to provide secretarial services, including clerical work for the Institutional Review Board (IRB), drawing up

contracts, and estimating the costs of clinical trials. The second major function is to introduce the clinical research coordinator (CRC), who acts as a cooperater at the site of clinical research.

The role of the CRC is to support clinical research with an emphasis on the principles of GCP, such as protecting the rights of patients and assuring the reliability of data. The CRC is involved in every step of a clinical trial. As understanding of the role of CRCs has deepened, requests for the introduction of CRC to the clinical trials have been increasing the number of personnel in the Clinical Research Office

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have been increasing. However, the circumstances of clinical trials are changing rapidly and new problems have arisen. To carry out more high-quality clinical trials in the future, we would like to explain clinical trials and the work of CRCs and describe the present status and future problems at The Jikei University Hospital from the point of view of CRCs.

#### **DUTIES OF THE CLINICAL RESEARCH OFFICE**

The Clinical Research Office was established as an administrative unit under the immediate direction of the hospital director and functions as the secretariat of clinical trials and of the IRB. Its six main duties are as follows :

##### *1. Preparation of written standard operating procedures*

Each medical center offering a clinical trial service should prepare a detailed rulebook on the standard operating procedures (SOPs) so that trials can be performed uniformly. The medical center should conduct clinical trials in accordance with these SOPs.

##### *2. Preparation for and opening of hearings*

To help the IRB function efficiently, the Clinical Research Office performs a preliminary review of each new application for a clinical trial and confirms that all the necessary documents have been submitted and the protocol has been properly drawn up.

##### *3. Duties as clinical trial secretariat and IRB secretariat*

The clinical trial secretariat performs clerical work for the performance of clinical trials in accordance with the Pharmaceutical Affairs Law, GCP, and the SOP. It also functions as the IRB secretariat to help the IRB function smoothly.

##### *4. Dealing with clerical work involved in running clinical trials*

The Clinical Research Office draws up contracts for clinical trials, deals with clerical work arising from clinical trial from start to finish, and deals with monitoring and auditing by the sponsor.

##### *5. Taking custody of recordings and documents*

The Clinical Research Office takes custody of original data, written contracts, protocols, IRB-related documents, records concerning the supervision of investigational drugs, and other operational records and documents for a period specified by GCP.

##### *6. Duties of the CRC*

#### **ROLE OF THE CRC**

Medical centers complying with the ministerial ordinance on "New GCP" are obligated to introduce into their organization medical workers who cooperate in clinical trials under the guidance of principal investigators and subinvestigators<sup>1</sup>. These cooperators are generally called CRCs. The role of the CRC is based on the concept of GCP. That is, the CRC is responsible for improving the quality and reliability of data and protecting the rights and welfare of subjects. In consideration of their role as a mediator between patients and doctors or other operators, many centers have chosen nurses as the health-care professional best able to fulfill the role of CRC. At The Jikei University Hospital too, nurses have been appointed as CRCs, as have pharmacists who have dealt with contracts and have supervised investigational drugs.

Pharmacists and nurses have received different training and play different roles in hospitals, but they began to cooperate under clinical-trial protocols in such a way that their skills complement each others for a unified purpose. The CRC is a new position that serves as a liaison between doctors and patients and among the staffs of different departments and coordinates all activities concerned with a clinical trial to ensure its proper execution. Although CRCs

must perform all tasks, except exercising medical judgment, to support investigators throughout clinical trial, their most important duties or goals are :

- (1) Ensuring the ethics, scientific standards, and reliability of clinical trials
- (2) Ensuring the safety, rights, and welfare of subjects.

In practice, the following activities are involved :

- (1) Patient education, counseling, and observation
- (2) Cooperation with investigators
- (3) Explanation and guidance for medical staff involved in the clinical trial
- (4) Collection and supervision of patient data, preparation of case-report forms
- (5) clerical work involving documents and records necessary for clinical research.

The actual work varies slightly according to the objective, design, and duration of the clinical trial, the target disease, and the number of subjects but usually involves every aspect of the clinical trial from start to finish.

#### STATE OF CRC WORK AT THE JIKEI UNIVERSITY HOSPITAL

When the Clinical Research Office was first established, many problems were encountered, such as clinical trials that were to be conducted under the old GCP and doctors performing clinical trials who had only a superficial knowledge of the new GCP or were not familiar with the role of the CRC as a cooperator for the clinical trial. Although a briefing was held about the new GCP at The Jikei University Hospital immediately before the opening of the Clinical Research Office, many doctors likely took a “wait and see” attitude. In 2000, approximately 40% of all contracts for clinical trials at The Jikei University Hospital were assigned to the department of internal medicine (Fig. 1), and the rest were allocated to 8 other departments.

To introduce CRCs at The Jikei University Hospital, the principal investigator submits a request, after which the Clinical Research Office staff deliberate, then decide when and how to introduce a CRC. Such a procedure was necessary at first, because the

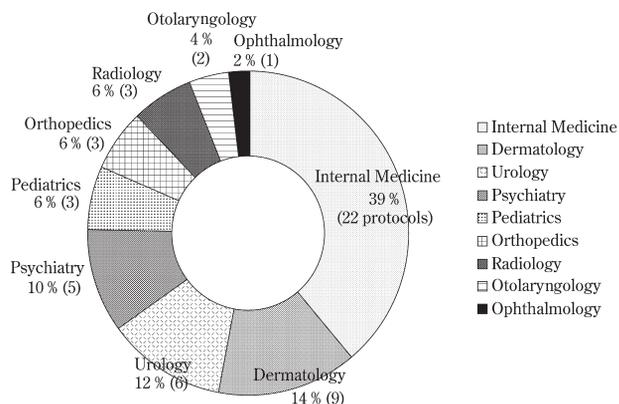


Fig. 1. Contracts of registration trials according to clinical department in 2000

Clinical Research Office had difficulty taking part in all clinical trials when its staff comprised only 1 full-time and 2 part-time coordinators and because doctors had to be persuaded to regard CRCs as members of the clinical trial team. Thus, CRCs were introduced to 29% of all clinical trials.

The rate of participation in clinical trials (the percentage of subjects who are actually registered) was 75% in CRC-coordinated clinical trials but was 53% in non-CRC-coordinated clinical trials (Fig. 2). The reason why the application rate fell short of 100%, even when CRCs had been introduced, was that the protocol was not likely to attract many patients at The Jikei University Hospital because of the target disease and of the inclusion criteria and that the contract or introduction of the CRC occurred immediately before registration for the clinical trial.

After several clinical trials had been conducted, cooperation between doctors and CRCs, work sharing, and the system of cooperation with the field staff were gradually understood, and the number of CRC-coordinated trials has been increasing. Now, nearly all protocols involve outpatients, and although the frequency of visits by subjects varies from trial to trial, the number of visits was approximately twice as great in 2000 as in 1999 (Fig. 3) and is expected to increase further in 2001.

#### PROBLEMS IN THE RUNNING OF CLINICAL TRIALS

Although we have participated in clinical trials as

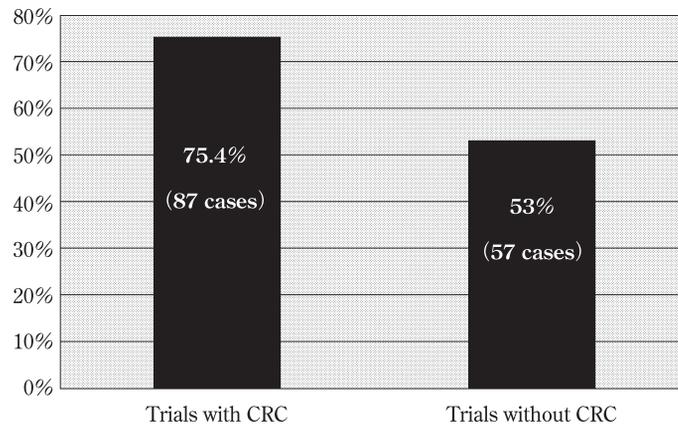


Fig. 2. Enrollment rate of subjects in registration trials in 1999

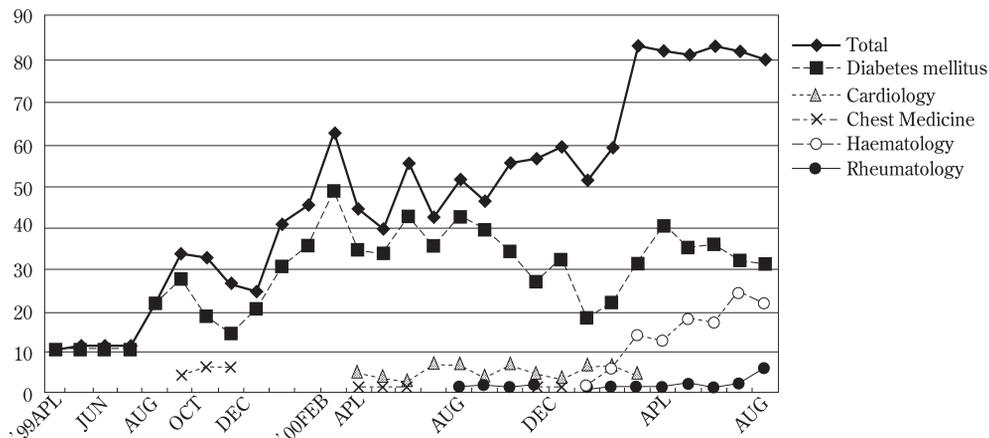


Fig. 3. Number of patient visits per month in 1999 and 2000

CRCs and dealt with various problems for only a short time, the circumstances of clinical trials are rapidly changing, as is medical practice in general. The following are some problems we are particularly concerned about.

#### 1. Recruitment of trial subjects through mass media

After "Management of Information About Recruitment of Trial Subjects" was issued by the Ministry of Health, Labor and Welfare's Pharmaceutical and Food Safety Bureau, Safety Division, in December 2001 recruitment information for trial subjects could appear in the mass media. Since then, numerous subject-recruiting advertisements have appeared in newspapers and on the Internet.

The Jikei University Hospital uses posters within

the hospital and advertisements in newspapers to recruit subjects for clinical trials. Because hospital posters provide trial information to patients already cared for at The Jikei University Hospital and their families, if a patient in this hospital wants to participate in a clinical trial, we can verify information about the patient's illness, history, treatment and progress with the attending physician or the patient's chart.

However, verifying background information of prospective subjects who respond to advertisements in the media is difficult. Generally, when trial information is advertised in newspapers or other media, the applicant contacts the university call center. The call center operator briefly confirms that the applicant qualifies for participation in the clinical trial and introduces the applicant to the medical center dealing

with that trial. The medical center prepares for the prospective subject's visit and verifies background information related to the treatment. Both doctors and prospective subjects are conscious that the visit is for participation in a trial, which tends to limit the doctor's explanation about the treatment under trial, with little reference to general treatment procedures. The subjects also expect much from the trial and sometimes come to the recruiting center without consulting the attending physician. Should they do so, the CRC must create a trusting relationship between the doctor and the subject and ensure that the subject would feel safe coming to the hospital both for the clinical trial and for general purposes.

More frequently than generally realized, a patient is unsuitable for the trial. Because the call center cannot confirm the patient's background in detail, the patient's failure to meet inclusion criteria might be found only on examination and interview by the doctor. Patients may also reconsider their decision to participate in the trial after they have heard a detailed explanation from the doctor or the CRC.

Accordingly, to select suitable trial subjects despite limited background information, researchers must pay careful attention to the design of clinical trials and attempt to predict and prepare for the effects of advertisements in the mass media. There should be a sufficient exchange of information among sponsors, doctors, and CRCs, and the timing and content of advertisements, the status of clinical trials at other medical centers, and previous problems and measures taken should be carefully reviewed.

Events that can occur in response to advertisements must be considered. For example, if many potential subjects apply for a single study, who would put them in order? Is preliminary screening necessary, such as history-taking by a doctor over the telephone before a candidate visits the hospital? How are expenses, such as the fee for the patient's first visit, explained at the call center? The CRC confirms the processes for the hospital visit and adjusts them if necessary so that the patient can smoothly reach the doctor's office. If such preparations are made, the patient can participate in the trial without anxiety, and doctors and other staff (such as

laboratory technicians and outpatient clinic staff) can start the trial in a relaxed mood.

## 2. *Selection of gifts to subjects, patient's diary, and other issues*

Gifts for the patient are prepared according to the type of investigational drug, the method of administration, and the self-care instructions. For example, if self-injection is required in a trial, the subject receives syringes and needles for self-injection, a pamphlet and video explaining their use, and a case or bag to carry the injection kit as a gift. In addition, to record the state of administration and changes in symptoms, various sizes and types of recording form are supplied as a "patient's diary." The protocol may require the subject to record daily changes in outcome measures, which can take considerable time and effort.

Subjects are burdened in various ways by participating in a clinical trial. They have extra responsibilities that are not required during ordinary hospital visits, such as observing the schedule for visits to the medical center's outpatient service and informing other departments that they are participating in a clinical trial and are receiving other drugs or counseling. Accordingly, the devices provided to the subjects should be as easy to use and as convenient as possible. If the subject is accustomed to using a specific device for self-measurement of blood glucose and self-injection, the CRC should arrange with the sponsor and investigator for the subject to continue using the devices. If a specific device is required for a clinical trial, the patient should be given documents explaining its use in simple terms. Although the format varies among different protocols, the patient's diary should be adapted for the target disease and the age of the subjects. For example, if most subjects are elderly, the diary should have large letters, tables, and figures that are easy to read. Devices that increase physical and mental burdens might influence the patient's decision to participate in a clinical trial.

If the subject is careful about changes in symptoms and can use the device in a way that is reflected

in the control of disease, participation in the clinical trial would lead to instruction in the self-control of disease. By explaining the meaning of the diary, which the subject has painstakingly filled, and how it reflects treatment, the CRC can instruct the subject how to review activities of daily life, diet, and rest, which can improve the subject's self-care ability. Such improvement may be considered a benefit of participation in a clinical trial.

### *3. Screening of subjects is a lengthy process*

At The Jikei University Hospital, the CRC is introduced after deliberation by the IRB, and the clinical trial is conducted after the startup meeting for the initiation of the trial. However, even when the meeting had been finished and the start of a clinical trial has been declared, too few patients might have been enrolled. In some studies nearly all patients may have to be excluded because screening by the investigator finds that the target disease is not severe enough for inclusion, that the patient is receiving drugs whose use is prohibited, or that laboratory findings meet exclusion criteria. Depending upon the target disease, there may not be enough patients who satisfy the inclusion criteria because only untreated or first-time patients are desired as subjects to avoid wash out of current drugs. In such a case, the first subject might not be enrolled until 2 to 3 months after trial preparations have been completed. Because all patients in The Jikei University Hospital cannot be screened owing to limitations in time and facilities, CRCs can help screen subject candidates listed by physicians. However, as the enrollment deadline approaches and the pool of potential subjects contracts, the doctors' enthusiasm for the study may wane despite enrollment being incomplete. To avoid such a situation, we suggest that the general patient population be routinely asked to participate in clinical trials. At present, information about the clinical trial is known to only some investigators in the relevant department, with little information being shared with the department as a whole or with paramedical staff. Trial sponsors use various means to recruit subjects, but placing informational posters only in the out-

patient clinic of the relevant department can attract the attention of only patients and other paramedicals. However, if clinical trial information were posted in other departments and places visited by many patients, a larger number of patients might consider participating in a present or future clinical trial. Other means could be used to attract the patients' attention, but the first tasks are to keep the clinical trial team, including the investigator, interested in the study and to provide information to ambulatory patients.

### *4. Adjustment of schedule for the clinical trial*

The subjects of approximately 85% of clinical trials at The Jikei University Hospital are outpatients. For this reason, follow-up examinations required by the protocol are adjusted to fit with the schedule for outpatient consultation. Nearly all outpatients visit the hospital at intervals of 4 weeks, but subjects of clinical trials may have to come more frequently. However, the allowable deviation from the examination schedule varies with each protocol and ranges from 2 days to 2 weeks. The examination conditions are explained along with other information when informed consent is obtained from the subject, and the feasibility of complying with these conditions is confirmed. However, if a subject cannot visit the hospital for a scheduled follow-up examination, the limited allowance for time deviations may be extremely inconvenient.

### *5. Adjustment of the work of CRC*

Our clinical research staff increased from 1 full-time and 2 part-time coordinators to 7 full-time and 3 part-time coordinators, but the number of protocols and subjects increased proportionately. The number of subjects who visit The Jikei University Hospital every month is now 80 to 90 but is increasing. These subjects are sometimes concentrated at a certain time. For example if laboratory examination items include a test requiring fasting, they have to visit the hospital early in the morning resulting in the concentration of patients. If the investigator is scheduled for am-

bulatory duty on a certain day and time, all subjects might come at that particular time. Once the clinical research schedule is instituted, changing the follow-up cycle might be impossible and adjusting the schedule might be difficult. To facilitate cooperation between CRCs, 2 or 3 CRCs are assigned to each clinical trial even if the target number of subjects is small. For this reason, each CRC must now oversee many protocols. The current situation is inefficient, because 7 to 9 trials might be in progress with 10 to 15 subjects each. Because each clinical trial progresses at its own pace, individual CRCs have different workloads. In an attempt to standardize the workload of CRCs, we have introduced a numerical system for evaluating workload which considers the number of subject visits and tests, items for observation, and instructions given by CRCs for drug self-administration. To improve efficiency we have also adopted a pair system in which only 2 CRCs are assigned to each protocol. However, this system must be considered further.

#### CONCLUSION

At The Jikei University Hospital, CRCs are yet not introduced for every clinical trial.

Some trial contracts were made before the opening of the Clinical Research Office, whereas some

investigators and sponsors do not wish for a CRC to be introduced. In fact, depending upon the design of the trial, doctors and field staff alone would be sufficient to conduct the trial. Support by a CRC would be important in clinical trials with a complicated protocol where the inconvenience to subjects and field staff is likely to be great. Even if a CRC is not introduced, they should help the doctors and paramedical staff involved in the clinical trial to share the trial information and carry out the trial without error. CRCs should improve their own ability as well as the care of subjects while playing an important role in properly coordinating the progress of a trial.

One of the important tasks of university hospitals, where the latest treatment, education and research are taking place, is assist in the development of new drugs. To assist in the development of better drugs without wasting precious data obtained through cooperation by the subjects, we have aimed to objectively assess the state of clinical trials at The Jikei University Hospital and improve the performance of clinical research.

#### REFERENCE

1. Uchida E. CRC in a university hospital (in Japanese). *Clin Eval* 2001 ; 28 : 256-61.