Activities of the Japan Medical Association’s Center for Clinical Trials

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Introduction
Clinical trials are the final stage in the process of development and application for approval of new drugs and medical devices. The environment in which clinical trials are conducted in Japan has been changing greatly during the past decade.

It has become difficult to carry out high-quality clinical trials in a timely manner and without undue expense, because of delays in developing a basis for their strict implementation under the Good Clinical Practice ordinance of the Ministry of Health, Labor and Welfare, an ordinance that must be followed when conducting clinical trials. As a result, clinical trials are increasingly being carried out overseas instead of in Japan, creating an outflow of clinical research and placing excessive restrictions on trials conducted in Japan.

As a result, the following problems have emerged:

1) Delays in the approval of new drugs, and therefore delays in the opportunity for patients to benefit from these drugs.
2) Difficulty in providing high-quality medical care because of delays in introducing new drugs that are already available outside Japan.
3) Adverse effects on the development of domestic industries.

Thus, the restrictions that have been placed on clinical trials are not at all favorable.

To stem this adverse trend and strengthen Japan’s ability to compete internationally in drug research and development, the Ministry of Health, Labor and Welfare issued a report in 2002 that outlines its vision for the pharmaceutical industry.

In this context, and in cooperation with the Ministry of Education, Science and Technology, a nationwide clinical trial 3-year activation plan was developed to include the following:

1) Construction of a large-scale clinical trial network
2) Improvement of the system for clinical trial implementation in medical institutions
3) Support for patients’ participation in clinical trials
4) Reduction of the burden of clinical trials imposed on companies
5) Promotion of clinical research as a whole.

As part of these governmental policies, the Japan Medical Association (JMA) set up the JMA Center for Clinical Trials (JMACCT) in 2003 to promote clinical trials in Japan. This project, supported by a grant-in-aid from the Ministry of Health, Labor and Welfare, is attempting to prepare a basis for the implementation of clinical trials in Japan by constructing a nationwide clinical trial network and providing support for so-called doctor-led clinical trials.

Organization of JMA’s Center for Clinical Trials

Although JMACCT was set up by JMA, it is financially independent of JMA and is organized...
mainly by a steering committee comprised of members appointed by the president of JMA. The Center has two external committees to ensure fairness and transparency in carrying out projects.

One of the two external committees is the General Planning and Evaluation Committee, which is in charge of comprehensive planning and evaluation processes necessary for the proper implementation of projects and their smooth progress. The other is the Technology Planning and Evaluation Committee, which carries out discussions of specific technical issues.

**Doctor-led Clinical Trials**

Doctor-led clinical trials will be described briefly in this section, as they represent a new form of clinical trials.

Clinical trials so far have been carried out by companies. Clinical trials conducted by an individual doctor were not authorized to have agents manufactured on commission by an outside entity or to receive supplies of non-approved drugs or devices from the manufacturer. This made it necessary for doctors trying to conduct a clinical trial to purchase drug samples within their limited research budget, thereby restricting the scope of studies. In addition, the results of such studies generally were not admissible for application for approval because the study did not meet the standards prescribed in the Pharmaceutical Affairs Law.

However, the Pharmaceutical Affairs Law, as amended in 2002, took effect on July 30, 2003, and as a result the planning and implementation of clinical trials, which previously had been the exclusive province of companies, was permissible for doctors and dentists, marking the initiation of doctor-facilitated clinical trials.

Certain drugs that have been proved effective on the basis of clinical experience in other countries are not yet approved in Japan because of the lack of potential profit for manufacturers. Another case may be that in which drugs are approved in Japan for certain indications but commonly are used for non-approved or uninsurable indications. Doctor-led clinical trials are expected to improve the quality of medical care if doctors themselves are able to plan and conduct clinical trials of such drugs. Such clinical trials may solve problems such as the use of drugs that are not covered by Japanese health insurance but are available through parallel import or drugs used for non-approved indications even though both doctors and patients are aware of this.

Nevertheless, questions have been posed from various quarters as to whether doctors who are engaged in daily clinical practice are capable of planning and conducting clinical trials. Various other issues also require solutions. The task of JMACCT is to try to resolve such issues and to support doctor-led clinical trials.

**Selection of Investigational Agents and Research Projects**

Approval for doctor-led clinical trials supported by JMACCT requires that the investigating doctor submit an application, which then will be reviewed in external committees before being approved as a research project. The investigational agent is chosen from among drugs recommended by various member societies of the Japanese Association of Medical Sciences, on the basis of the need for the drug in clinical medical settings. The candidate drugs recommended by member societies are listed on the web-site of JMACCT (in Japanese).

If an investigator wishes to examine one of the candidate drugs, he or she may submit an application to JMACCT for support in planning the clinical trial. At this stage, the protocol of the intended clinical trial, case report forms, an informed consent form, and other documents are prepared. The expenses incurred in using the clinical trial consultation services of the Pharmaceuticals and Medical Devices Agency (PMDA) can be covered by the research funds.

Once a plan has been developed for the clinical trial, the investigator can apply for JMACCT’s support in coordinating and managing the clinical trial. At this stage, the doctor, as the coordinating investigator, carries out coordination and management procedures prior to implementation of the clinical trial. If the application for the research project is approved at this stage, it is assured of being conducted.

**Construction of the Clinical Trial Network**

When the clinical trial of a particular agent is slated to take place, a site needs to be determined. The clinical trial network plays an
important role here. JMACCT constructs and maintains a large-scale, nationwide network for clinical trials.

Since its founding, JMACCT has invited medical institutions to register for inclusion in the network, under the following requirements: the institution is willing to participate in clinical trials, understands the meaning and structure of projects, and is able to cooperate in implementing clinical trials; the head of the institution agrees that the institution as a whole can apply for registration for including in the network and will respond to a brief questionnaire from JMACCT. This questionnaire is intended to ascertain the current situation of clinical trials in member institutions of the network as well as to inform the institution of what is required of medical institutions under the revised GCP. Medical institutions can apply to register at any time by going to the URL of JMACCT. About 800 institutions had registered with the network as of December 2004.

Medical institutions where doctor-led clinical trials supported by JMACCT are conducted are chosen from among member institutions registered with the clinical trial network. After it has been registered in the network, the member institution can receive information free of charge about clinical trials and notices of recruitment of institutions for company-supported clinical trials, in addition to being able to participate in doctor-led clinical trials for the adopted research projects.

Local Networks for Clinical Trials

JMACCT also supports local networks for clinical trials, which serve as branches of the large-scale clinical trial network, in the hope of enhancing the network. More specifically, 10 local networks were chosen in 2004 for research on the implementation of clinical trials. These networks include those of local medical associations, the National Hospital Organization, and universities.

Other Roles of JMACCT

JMACCT is taking various other actions to foster the smooth implementation of doctor-led clinical trials.

Development of model standard operating procedures

The first JMACCT activity is to develop model standard operating procedures. GCP prescribes that doctors who plan to perform a doctor-led clinical trial should prepare detailed, written operating procedures. It is not easy for doctors in daily clinical practice to prepare operating procedures by themselves, as operating procedures up to now have been prepared by companies that have sections specializing in this area. JMACCT supports doctors who wish to conduct clinical trials by preparing and publishing a template that can be used to describe operating procedures.

Compensation and liability insurance for doctor-led clinical trials

Another activity of JMACCT is that of developing compensation and liability insurance for clinical studies. GCP prescribes that in doctor-led clinical trials, doctors who carry out the clinical trial should provide some compensation for the study subjects. Compared with companies, it is more difficult for individual doctors to undertake compensation and liability measures. Therefore, JMACCT, in cooperation with an insurance company, has developed a new insurance service for doctor-led clinical trials. The insurance is available for doctors who carry out clinical trials of their own research projects, and the cost of insurance can be covered by the research funding.

Support for preparation of adverse drug reaction reports

If a serious adverse drug reaction occurs during a clinical trial, the investigator is obligated to report it to the national government. This is, however, not an easy procedure. For certain adverse reactions, the report needs to be submitted within 7 days of occurrence.

If an adverse drug reaction occurs in one of the participating institutions in a multicenter collaborative study, the investigator immediately must send information about the adverse reaction to other participating institutions, although appropriate treatment of the patient is certainly the first priority. Investigators of the various participating institutions also are obligated to file such reports. The reports should include detailed descriptions. To neglect this obligation may correspond to a violation of the Pharmaceutical
Affairs Law, and the clinical trial itself may be deemed as having been conducted unjustly.

JMACCT provides advice about the system used to report adverse drug reactions. This system provides smooth, safe transmission of information for each clinical trial. The Center is now developing software for adverse drug reaction reporting to facilitate the preparation of such reports.

**Development and maintenance of a basis for implementing clinical trials**

In addition to the above activities, JMACCT engages in various other projects to develop and maintain a firm basis for implementing clinical trials.

One of these activities was the “Industry-Government-Academia Joint Forum for the Promotion of Clinical Trials” held in November 2004 under JMACCT sponsorship. About 350 participants gathered in the JMA Hall to attend the forum.

Leading figures from various quarters participated as speakers or panelists. Panelists included Hatsuo Aoki, president of the Japan Pharmaceutical Manufacturers Association; Kazuhiko Adachi, head of the Research and Development Division, Ministry of Health, Labor and Welfare; Keiji Ueda, adviser of the Pharmaceuticals and Medical Devices Agency; Shigeyuki Nakano, chairman of the board of directors of the Japanese Society of Clinical Pharmacology and Therapeutics, as a representative of the academic sector; Yoshio Yazaki, chairman of the board of directors of the National Hospital Organization; and Mitsuko Ishii, an actress who has a nurse’s license, as a representative of the general public.

Audience opinion indicated that 80% of the participants expected clinical trials to be carried out more actively in Japan. Many participants also indicated that JMA should promote the participation of private medical practitioners in clinical trials and should foster a better understanding of clinical trials among the general public.

A better understanding of clinical trials by medical practitioners and their active participation in them were considered extremely important, particularly in promoting the development of agents for the treatment of lifestyle-related diseases, because many of the patients who have lifestyle-related diseases attend small and medium-sized medical institutions. To further educate doctors working in such medical institutions, JMACCT plans to issue a clinical trial-related textbook tentatively called “The ABC’s of Clinical Trials” by late 2005.

To educate the general public, promotional posters were sent to medical institutions throughout the country. In addition, by utilizing local networks for clinical trials, local citizens will come to have a better understanding of such trials.

**Future schedule**

JMACCT set up a new Data Management Section in February 2005 to manage data obtained not only from clinical trials of new drugs but also from clinical research on drugs available on the market. To play a role as a databank, in addition to supporting research, JMACCT is building a framework to foster the transmission of information from Japan to other countries.

**Health Care Administration and Clinical Trials**

Finally, changes in health care administration in relation to clinical trials need to be discussed.

In December 2004, the Ministry of Health, Labor and Welfare issued an agreement regarding the combined use of insurable and uninsurable health care services. In this context, the use of drugs not yet approved in Japan was taken up as an important issue, and major reform of the system was scheduled to take place within the current fiscal year, 2005. The following fundamental principles of this reform have been stated as follows:

1) Secure implementation of clinical trials
2) Development and maintenance of a support system for doctor-led clinical trials
3) Introduction of additional clinical trials
4) Combined use of health insurance treatment to avoid interruption in treatment

Thus, it is presumed that clinical trials will assume greater importance in improving the quality of medical care in Japan. JMACCT wishes to underline the importance of enhancing the support system for doctor-led clinical trials and to encourage the further development and maintenance of the basis for implementation of clinical trials, which are extremely important in Japan’s health care system. JMA as a whole intends to address this issue in a more active and aggressive manner.