

REVIEW

Research ethics committees in Japan : A perspective from thirty years of experience at Tokushima University

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Abstract : The first Japanese ethics committee for biomedical research involving human subjects was established at Tokushima University in 1982. Although this committee was not formed as a response to national directives, the government eventually developed ethical guidelines, such as the Ethical Guidelines for Clinical Studies that were established in 2003. The practical impact of such guidelines was a rapid increase in the number of protocols seeking ethics committee approval and, accordingly, an increase in the workload of ethics committees. This review describes the activity of the ethics committee at Tokushima University during the last thirty years and discusses the infrastructure that best supports the activities of this committee. In addition, we address the issues that ethics committees now face and discuss future directions. *J. Med. Invest.* 62 : 114-118, August, 2015

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INTRODUCTION

It is now widely acknowledged that reviews by independent ethics committees are essential for biomedical research involving human subjects. Tokushima University is located in Tokushima in the rural Shikoku region of Japan. The first ethics committee in Japan was established at Tokushima University in 1982 to review investigator-initiated biomedical research. Notably, this committee was not formed as a response to national directives. However, the government later developed ethics guidelines, such as the Ethical Guidelines for Clinical Studies that were established in 2003. This changed the situation at the national level, and reviewing research ethics became a key process in institutions that conduct biomedical research.

In this review, we describe the activity of the ethics committee at Tokushima University during the last thirty years. In addition, we discuss the infrastructure that best supports the activities of this committee, such as set-up of the Academic Office of the Ethics Committee, research ethics education seminars, and research ethics consultations. Finally, this article addresses the issues that ethics committees now face and discusses future directions.

THE FIRST ETHICS COMMITTEE IN JAPAN

The first ethics committee in Japan was proposed at Tokushima University by a fertility researcher. As background, we note that sterility is a serious problem, and in vitro fertilization (IVF) is a medical procedure that was developed to overcome sterility. Although IVF is currently a well-established clinical practice, it was an innovative therapy back in the 1970s (1). The procedure was developed in the United Kingdom by Steptoe and Edwards, and in July 1978, Louise Brown became the world's first "test-tube" baby. In April of 1981, Prof. Takahide Mori arrived at Tokushima

University School of Medicine as a Professor in the Department of Gynecology and Obstetrics. His focus was IVF research, and he began to establish a laboratory and to train physicians. In September of 1982, the department prepared to offer in vitro fertilization as a clinical procedure at Tokushima University. Although Prof. Mori was quite confident that IVF was an appropriate procedure from both a clinical and a patient viewpoint, he was aware that a physician's confidence alone is not sufficient for pioneering innovative therapy—societal approval is needed as well. To ensure this, he discussed the matter with Prof. Takao Saito, the Director of the Hospital, and with Prof. Masuhide Miyao, the Dean of the School of Medicine. They agreed that it would be appropriate to set up an ethics committee to ensure that the research was acceptable from a societal point of view.

On December 14, 1982, the Ethics Committee of Tokushima University School of Medicine held its first meeting. The Committee consisted of 8 members. These were dean of the school of medicine, director of the university hospital, 2 professors of basic medicine, 2 professors of clinical medicine and 2 academic experts other than medicine (2). Over the course of 11 meetings, 11 external specialists were invited to attend. Although the original goal of the committee was to ensure the social acceptability of proposed research, ethical issues such as respect for persons, beneficence, and justice were also considered during the review process. On April 12, 1983, the committee approved the proposed IVF project, and in March of 1984, the third "test-tube" baby in Japan was born at Tokushima University.

THE ETHICS COMMITTEE IN THE 1980s AND 1990s IN JAPAN AND AT TOKUSHIMA UNIVERSITY

After the establishment of the Ethics Committee of Tokushima University School of Medicine, the number of ethics committees gradually increased in Japan. It is notable that ethics committees were not mandatory in medical schools. Like Tokushima University, one motive for establishing separate ethics committees at each medical school was to deal with some difficult problems that physicians had never faced before. Sakai suggested other motives as well (3). One motive was to address issues related to conforming

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to the tenants of the Declaration of Helsinki. Second, developments in the United States made Japan realize that the clinical applications of new medical technologies needed prior review by each research institution.

To assess the state of ethics committees in Japan in the early 1990s, Saito (4) surveyed 80 medical schools by questionnaire in 1991 and reported that ethics committees had been established in 79 of the 80 schools. He considered it fortunate that committees were established voluntarily by members of each campus rather than in response to national directives or legislation.

In 1992, ten years after the establishment of the Ethics Committee of Tokushima University School of Medicine, another committee was established at the University Hospital as a sub-committee of the Ethics Committee of Tokushima University School of Medicine. The sub-committee at Tokushima University Hospital did not deal mainly with urgent issues, such as those posed by IVF, but with more ordinary issues in medical practice and research. Gradually, the number of protocols seeking ethics committee approval increased.

TWO MAJOR CHANGES IN THE REGULATION OF CLINICAL STUDIES THAT OCCURRED AROUND 2000 IN JAPAN

From a regulatory viewpoint, there were two major changes around 2000 in Japan in the field of biomedical research involving human subjects. The first was a change in clinical trials for drug approval, also called registration trials, which are regulated by pharmaceutical laws. In 1998, Good Clinical Practice (GCP) guidelines, which were originally approved by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), were deployed for all registration trials. Prior to this, most university hospitals had different types of committees for reviewing registration trials, and they had to revise these committees to conform to GCP guidelines. At Tokushima University Hospital, the structure and management of an already-established committee (which was separate from the Ethics Committee of Tokushima University Hospital) was substantially altered and strengthened.

The second change was the establishment of ethics guidelines by the appropriate government ministries (5). These guidelines apply to clinical studies other than registration trials. The Japanese

government enforced the Ethical Guidelines for Human Genome and Gene Analysis Research as guidelines for research in 2001; the Ethical Guidelines for Epidemiological Research were enforced in 2002, and the Ethical Guidelines for Clinical Studies were enforced in 2003. The applicable research fields were designated by these guidelines, and ethics committees that had been established voluntarily became mandatory for medical institutions that conduct these types of research. Accordingly, from a practical standpoint, matters related to the maintenance of ethical committees had to be addressed by each institution. Notably, even at present, GCP is not applied to clinical studies other than those related to the approval of drugs and medical devices, except for regenerative medicine. As for regenerative medicine, a new safety law was passed in 2013 and will be enforced in 2014. In addition to ensuring the safety of regenerative medicine, this new law and other related Japanese policies focus on providing a fast-track approval process for stem cell therapies (6).

THE ETHICS COMMITTEE AND ESTABLISHMENT OF THE ACADEMIC OFFICE OF THE ETHICS COMMITTEE AROUND 2000 AT TOKUSHIMA UNIVERSITY HOSPITAL

In response to enforcement of these guidelines in 2001-2003, the number of protocols increased (Figure 1). Although the Ethics Committee had an administrative division (section of the administrative office of Tokushima University Hospital), additional infrastructure was needed to support it. The increased workload was observed in Japanese ethics committees at other institutions as well (7).

In addition, to provide infrastructure for registration trials and to comply with the GCP guidelines, the Clinical Trial Center for Developmental Therapeutics (CTCDT) was established in April of 1999 at Tokushima University Hospital. Originally, the CTCDT aimed to manage and promote registration trials by liaising with clinical research coordinators (8) and by educating investigators about registration trials. The CTCDT was set up to meet the requirements of the various ethics guidelines, and in July of 2002, the Academic Office of the Ethics Committee was set-up as part of the CTCDT. Subsequently, in October of 2003, the sub-committee was renamed the "Ethics Committee of Tokushima University

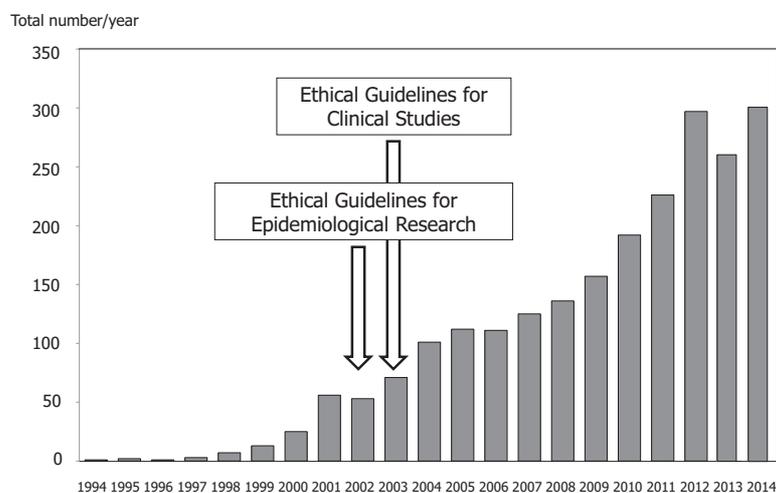


Figure 1
The annual number of protocols submitted to the Ethics Committee of Tokushima University Hospital.

Hospital" and became the main committee for reviewing biomedical research involving human subjects, including investigator-initiated clinical trials.

THE CURRENT STATUS OF THE ETHICS COMMITTEE AND THE ACADEMIC OFFICE OF TOKUSHIMA UNIVERSITY HOSPITAL

The Ethics Committee of Tokushima University Hospital consists of 13 members. Of these, 5 are from outside the institution and 2 are women, and the member system is set in accordance with governmental ethical guidelines. Meetings are held monthly and have the Office for Human Research Protections (OHRP) registration number. As shown in Figure 1, the number of protocols submitted annually to the ethics committee at Tokushima University Hospital continues to increase.

The Academic Office of the Ethics Committee works with specific section of the administrative office of Tokushima University Hospital. One medical doctor, two scientists, and one officer, none of whom are committee members, have roles at the Academic Office of the Ethics Committee. The aims of the Academic Office of the Ethics Committee include administrating the proceedings of the ethics committee, providing ethics education to investigators in collaboration with the ethics committee under the supervision of the director of the hospital, advising investigators, and conducting pre-checks of documents. Pre-checking documents by the Academic Office takes about 5-6 hours per protocol. The main objective is not to review the protocols per se, but to suggest ways for the investigators to facilitate the review process and make the review process more efficient. For example, the status of clinical trial registration for interventional studies (9) is checked by the Academic Office before ethics review by the committee. In practice, the Academic Office sometimes suggests additional information that may be needed or suggests revision of the documents.

To ensure compliance and the ethical conduct of clinical studies, each Japanese institution established a department that works closely with their ethics committee. Some issues face these departments, such as how to deal with new issues, staff shortages, the career path of the staff, and how best to ensure that the staff remains up-to-date.

RESEARCH ETHICS EDUCATION AND CONSULTATION AT TOKUSHIMA UNIVERSITY HOSPITAL

Similar to institutional review boards in the United States, ethics committees in Japan are involved with reviewing research protocols. In addition, they are also in charge of developing policy, education, and consultation, which is similar to hospital ethics committees in the United States (7). In 1995, a survey of ethics committees at Japanese medical schools showed that 17.5% offered consultations, and 21.3% provided educational resources to investigators (7). We use two major approaches in ethics education for investigators at the University Hospital. First, we have our investigators registration rule and offer educational seminars regularly. Second, the Academic Office advises investigators via research ethics consultations.

The registration rule for physicians was originally established in 2001 in response to the GCP, and it was aimed at maintaining the quality of registration trials at Tokushima University Hospital. In the rule, attendance at a clinical trial seminar became mandatory to be selected as an investigator for registration trials.

In 2009, the revised Ethical Guidelines for Clinical Studies came into effect, and coverage of our registration rule was expanded in order to maintain the quality of investigator-initiated studies at

Tokushima University Hospital. According to the new rule, attendance at a clinical trial seminar became mandatory for all investigators requesting research review by the Ethics Committee of Tokushima University Hospital.

Clinical trial seminars began in 2000 for investigators at Tokushima University. Practically, we accept participation of investigators outside Tokushima University and we started to enlighten that seminars are open to all investigators outside Tokushima University in 2006. Regular seminars are held monthly by the staff of the CTCDT, and face-to-face contact at the occasion is encouraged for future partnerships between investigators and the staff of the CTCDT. The seminars address the scientific and ethical aspects of clinical studies and offer practical tips for requesting research review by the Ethics Committee of Tokushima University Hospital and for conducting clinical studies at Tokushima University. In addition, seminars by specialists are held 4-6 times per year. Figure 2 shows the annual number of participants in the clinical trial seminars; it is clear that the number increased rapidly after expansion of the rule. Most participants are investigators at postgraduate level. Although undergraduate investigators are encouraged to attend these seminars, closer cooperation with undergraduate ethics education remains as an important issue. Similar educational systems are operated, for example, at the institute and medical organization levels, and recent attention has been focused on the establishment of nationwide system or authorization in Japan.

The Academic Office of the Ethics Committee provided advice to a total of 950 inquiries from investigators in 2014. Most of these were investigators in clinical departments, but some came from other departments, and a few came from outside of Tokushima University. The consultations were mainly regarding administrative matters, with consultations regarding research itself accounted for about 10%. To respond more effectively to investigator inquiries, we set up regular time for research ethics consultations in 2012. Although research ethics consultations are now common in the United States (10, 11), only a small number of institutions in Japan offer this service (12). We provided 30 research ethics consultations in 2014. Accordingly, promoting and maintaining high quality research ethics consultations remains an important issue at Tokushima University Hospital as well as at other Japanese research institutions.

In 2012, we celebrated 30 years of ethics committee in Tokushima University by holding a special symposium focusing on research ethics education in the new era. After Prof. Reidar K. Lie of the University of Bergen gave a special lecture about the global status of research ethics, other invited Japanese leaders in research ethics education (Drs. Yutaka Matsuoka, Fumitaka Nagamura, Kenji Matsui and Shimon Tashiro) discussed the challenges in research ethics that face investigators. We consider communication among those who play important roles in research ethics education and consultation to be very important for the acceptance and use of research ethics committees.

BIOMEDICAL RESEARCH IN JAPAN AND FUTURE DIRECTIONS FOR ETHICS COMMITTEES

Japanese biomedical research now faces the repercussions from a major scandal. Briefly, data related to a blockbuster hypertension drug was manipulated in a multi-institutional clinical trial, and exposure of this manipulation resulted in the retraction of published papers (13). Currently, even for clinical trials conducted from the interest of industry, GCP does not apply outside drug approval scheme (14), and Japan has no national system to ensure research integrity. Research misconduct may lead to violent protests to protect research participants; thus, each ethics committee must take active steps to remedy the current situation.

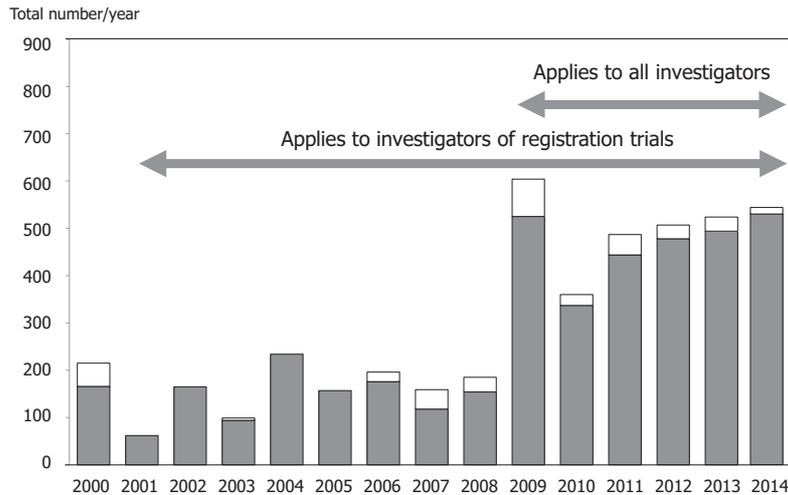


Figure 2

The annual number of participants in clinical trial seminars hosted by the Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital.

The shaded regions of the columns represent participants from Tokushima University, while the white regions represent participant from other institutions.

We must also work to ensure that the ethics committees provide sound, high quality guidance to researchers. Although the structure and function of ethics committees are basically defined by governmental ethics guidelines, the system that ensures the quality of ethics committees is still unsatisfactory in Japan. For example, no one even knows the exact number of ethics committees in Japan. In 2012, the Ministry of Health, Labor and Welfare initiated a registration system for ethics committees, and voluntary registration is encouraged. According to the registration system website (15), a total of 1422 ethics committees were registered as of May 1, 2015, which seems like quite a lot of ethics committees, and governmental certification of ethics committees has now begun in 2015. Until now, each institute and hospital has established their own ethics committee, but we are now discussing whether it would be useful to have a single ethics committee for use by several institutions in order to offer high quality advice and education.

As for the situation in the Tokushima prefecture, Tokushima University Hospital established the Tokushima Network for Clinical Trials in collaboration with the Tokushima Medical Association in 2004 (16) in response to a plan for promoting registration trials by the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology of Japan. The investigator registration rule now applies to registration trials at medical institutions that are in the same network as Tokushima University Hospital, but it does not cover all clinical studies.

In several countries in Europe, region-based ethics committees, which are called local research ethics committee, play roles in the ethical conduct of research (17). Although it is possible for local investigators to seek an ethics review from committees that are part of medical organizations (18), especially medical clinics, it seems appropriate that the ethics committee of a university hospital also act as a local research ethics committee i.e. provide education and consultation services to other, perhaps smaller, local institutions. In a survey of the performance of clinical studies and ethics committees in Tokushima prefecture, 170 medical institutions cite the following primary reasons for a lack of experience in conducting clinical research : no arrangement with an ethics committee, no interest in clinical research, a lack of available assistants, and no opportunity to participate in clinical research (19). Because of

the voluntary nature of ethics committees when they were first established, Japanese ethics committees often lack robust financial support. These practical issues, i.e. access to ethics committees and financial support, must be addressed, and communication between hospitals and clinics that are part of the “Tokushima Network for Clinical Trials” will serve as the foundation for this to happen.

Recent attention has been focused on the functions of ethics committees at post-approval phase. In the first place, the post-approval state of each study was not monitored in most institutions. We started annual status survey of approved studies in 2003 prior to the indication by the revised Ethical Guidelines for Clinical Studies in 2009. Nevertheless, the contribution of ethics committee to post-approval issues is not still satisfactory. System that enables ethics committees to contribute effectively to post-approval issues, such as adequate publication securing research integrity, ancillary care and proper returning of study results to participants, should be established.

CONCLUSIONS

Thirty years ago, investigators at Tokushima University who were trying to popularize IVF, then a new medical procedure, established a system for the ethical conduct of biomedical research. In preparing of this manuscript, two governmental guidelines, the Ethical Guidelines for Epidemiological Research and the Ethical Guidelines for Clinical Studies, have been integrated and new guidelines, the Ethical Guidelines for Medical and Health Research Involving Human Subjects (20), were enforced in 2015. After considering the history and experience of this committee, we continue to try to optimize the system to ensure oversight of the ethics of biomedical research in Tokushima Prefecture based on the new guidelines. This system may be appropriate for adaptation and use throughout Japan and even worldwide.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest related to this article.

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