Chapter 8
Research Regulations, Ethics Committees, and Confronting Global Standards

Abstract Japan's modern system of scientific governance was imported from the West. Starting with the The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good clinical practice (ICH-GCP).

Japan needed to institute best global practice in order for Japanese research and pharmaceutical products to be recognized on the world stage. However, because the scientific governance system was imported, there was a mismatch between the basic concepts and underlying intentions of the system and Japanese culture.

The lack of competent ethics committee members and ethics consultation support infrastructure in Japan is a serious concern. Scientific misconduct is a universal phenomenon; however, I will explore it here in the local context. Finally, I will illustrate how the advice by clinical ethics consultations differs from culture to culture, although the formats (individuals, teams, and committees) are the same.

Japan imported research regulations from the West, driven by concern that if it did not meet international standards, then its medical research and drug development would not be respected. The earliest established protocol was the Good Clinical Practice guidelines (GCP, 1989) that regulated drug trials. Japan revised its standards to be consistent with those of the GCP (ICH-GCP) issued at the International Conference on Harmonization in 1997 in order to align with those of the USA and EU.

8.1 Governmental Guidelines or Legislation?

In Japan, most research regulations established by governmental administrative guidelines are not legally binding. In addition, these guidelines were created by each governmental department to target various research procedures and medical care. Japan has a tendency to avoid legislature, primarily because establishing new legislation in Japan is incredibly difficult, and once established, it is then very dif-

A. Akabayashi, *Bioethics Across the Globe*,
https://doi.org/10.1007/978-981-15-3572-7_8

ficult to change. On the other hand, administrative guidelines are flexible and can be changed, adapted, or adjusted. Because those who breach guidelines are penalized by strict sanctions such as loss of public funding, administrative guidelines are considered powerful within Japan. However, administrative guideline regulations have been applied unsystematically, and a new regulation is created for a given research field or medical procedure every time a new issue arises.

Consistency between guidelines is also problematic, leading to confusion onsite. The Japanese government structure is one of "vertical segmentation," in which the roles of each governmental agency are specified and problems are addressed with low rates of collaboration and slow methodology through interrelationships between multiple agencies. In such a system, guidelines are often produced independently by different ministries (e.g., the Ministry of Health, Labour and Welfare (MHLW), the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Ministry of Trade, Economy and Industry (METI), to name a few) and relevant departments, leading to further confusion. Because of these problems, some recent guidelines have been issued by multiple ministries; this is a positive trend [1] (Table 8.1).

8.2 Ethics Committees in Japan

I have served as the Chair of the human research ethics committees at Kyoto University (4 years) and University of Tokyo (16 years). In what follows, I draw, in part from my own experience.

8.2.1 Number and Status of Ethics Committees

The first ethics committee in Japan was established in 1982 at Tokushima University Medical School.

The number of ethics committees at universities and hospitals conducting research in Japan increased dramatically as the twenty-first century began (Fig. 8.1) [2], due to the fact that administrative guidelines noted above required the establishment of an ethics committee within each institution.

The ethics review committee system was created on a voluntary basis at each institution during the initial phase (1980s to 1990s). Some were independent, approving research protocols. Some were involved in designing hospital policies for new technology. By the time the government administrative guidelines were established in 2000, research ethics committees are clearly designated as an

Table 8.1 Recent guidelines on scientific and ethical standards in Japan

Year	Administrative legislation	Affiliated ministry(s)[a]	Classification
1989	Guideline for good clinical practice (GCP)	MHW	Circular
1994	Guideline for clinical research on gene therapy	MHW	Notification
1996	Pharmaceutical affairs law (amended)		Law
1997	New guideline for good clinical practice (New GCP)	MHLW	Ministerial ordinance
1997	Organ transplantation law		Law
2000	Human cloning prohibition law		Law[b]
2001	Ethics guidelines for human genome/gene analysis research	MHLW, MEXT, METI	Notification
2001	Guideline for derivation and utilization of human embryonic stem cells	MEXT	Notification[b]
2001	Guideline for the handling of human embryos for research	MEXT	Notification[b]
2002	Ethical guideline for epidemiological research	MEXT, MHLW	Notification
2002	Guideline for clinical research on gene therapy (amended)	MEXT, MHLW	Notification
2002	Public health guidelines on infectious disease issues in xenotransplantation	MHLW	Notification
2003	Privacy protection law		Law
2003	Guideline for clinical research	MHLW	Notification
2004	Ethical guidelines for epidemiological research	MEXT, MHLW	Notification
2014	Guidelines on the derivation of human embryonic stem cells	MEXT, MHLW	Notification
2014	Guidelines on the distribution and utilization of human embryonic stem cells	MEXT	Notification
2014	Abolishing guidelines on clinical research using human stem cells	MHLW	Notification
2014	Ethical guidelines for medical and health research involving human subjects	MEXT, MHLW	Notification
2017	Clinical research act		Law

[a]*MHW* Ministry of Health and Welfare, presently the Ministry of Health, Labor, and Welfare; *MHLW* Ministry of Health, Labor, and Welfare; *MEXT* Ministry of Education, Culture, Sports, Science, and Technology; *METI* Ministry of Economy, Trade, and Industry

[b]English translations are available online: Human Cloning Prohibition Law (http://www.mext.go.jp/a_menu/shinkou/seimei/2001/hai3/4_houritu.pdf);
Guideline for Derivation and Utilization of Human Embryonic Stem Cells (http://www.mext.go.jp/a_menu/shinkou/seimei/2001/es/020101.pdf);
Guideline for the Handling of Human Embryos for Research (http://www.mext.go.jp/a_menu/shinkou/seimei/2001/hai3/31_shishin_e.pdf)

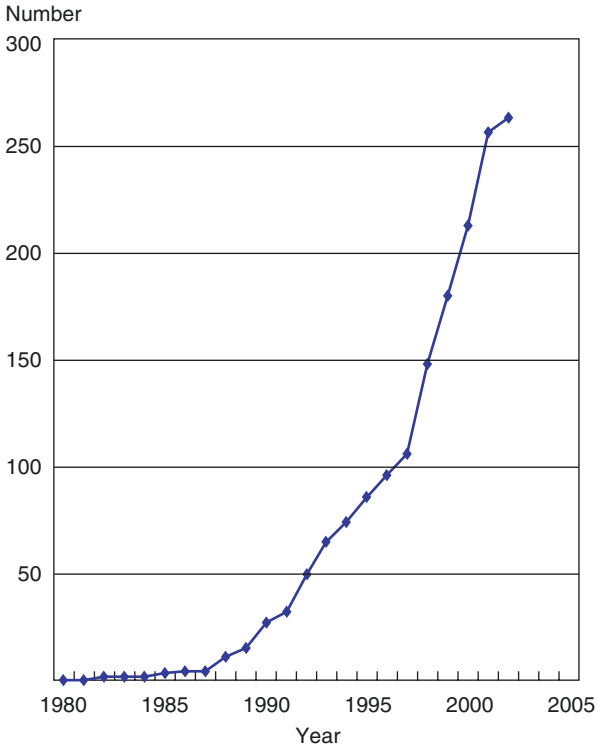


Fig. 8.1 The number of ethics committees established at general hospital in Japan

advisory body for the Dean or hospital director, and all research using human participants, or their material and data, are approved by research ethics committees.

8.2.2 Ethics Committee Members and Their Roles

Most research ethics committees operate voluntarily with regard to funding. Universities and institutions pay only small honoraria for external committee members. Internal members like myself have not received any recompense. I have chaired ethics committees for 20 years in a voluntary capacity. During that time I was on-call (24/7, 365 days a year) to confirm that informed consent of potential recipients of brain-dead liver transplants at Kyoto University Faculty of Medicine had in fact been given (See Chap. 2). In some instances I was called at 1:38 AM and had to be at the hospital by 5:00 AM (Fig. 8.2). Transportation costs were not covered by Kyoto University Hospital.

Fig. 8.2 Times the Chair of the ethics committee was called to confirm final informed consent recipient candidates from brain-dead donors

In order to create an ethics committee in accordance with the governmental guidelines, every committee needs to seek one or two lay committee members. We must ask, therefore, what is the role of the lay member? The ethics review system in the USA developed against a backdrop of racial discrimination and an inadequate level of patient advocacy. Therefore, ethics review committees required participation by persons who represented the perspective of the general public.

Japan imported this system and began using it without understanding this history or cultural context. Japan is a nation that is relatively racially homogeneous and has not faced a history of slavery or segregation. In addition, in the established system (Clinical Research Act, 2017) [3], patient rights were to be represented by a lawyer or someone with an understanding of bioethics.

My search for lay committee members has resulted in a professor emeritus several years into retirement, a retired employee of a pharmaceutical company, a principal of elementary or junior high school, a Buddhist monk, and a homemaker.

Within the flexible limitations of the administrative guidelines, each institution exercised discretion in determining their own suitable layperson committee member. This caused other problems, as described in the next section.

When recruiting lay committee members, many candidates asked me, "What am I supposed to do?" In response I suggested that they "Put yourself in the shoes of a patient or research participant, and when the explanation form or consent form is difficult to understand, or when you might, as a patient or participant, have a gut feeling that something is wrong, just speak up and say so."

The complexities are illustrated by this example: One lay committee member claimed that an informed consent form was difficult to understand. I listened carefully and suggested many changes. After spending some time reviewing it, she still claimed that it was unclear. I then asked her, "What changes do you think the researchers need to make to this part you mentioned?" She still had no answer and was unable to suggest an adequate alternative.

This phenomenon is not limited to lay members of ethics committees. For example, committee members from outside the university with backgrounds in biology ask questions in accordance with their own scientific interest, or simply display their knowledge.

In sum, many committee members did not understand what they were to discuss. It did not help that very few opportunities were available in Japan where these members could receive education about their role as ethics committee members.

8.3 Enforcement of the Clinical Research Act

The most recently established regulation is the Clinical Research Act (CRA), enacted in 2017 as cited above [3]. This law was created primarily in response to an incident of research misconduct that came to light in a collaborative research project between a university and corporation, in a manner similar to that of the Diovan incident [4].

This Act targets *only* specified clinical trials, which are:

1. clinical trials for pharmaceutical products that are either not yet approved or not approved for the particular purpose by the Pharmaceutical and Medical Devices Law
2. clinical trials for pharmaceutical products from a pharmaceutical company conducted with funding from the pharmaceutical company

The government explained that the reason the law applied only to specified clinical trials is that "excessive regulation can result in a weakening of freedom of research, so only a portion is subject to regulation." However, of the many types of studies being conducted, the law was applied only to two kinds of clinical trials, and the government required the independent establishment of a law-based institutional review board (*Nintei Rinshō Kenkyū Shinsa Iinkai*; hereafter, Certified Review Board: CRB) separate from the research ethics committees. This significantly increased the number of forms needed to report back to the government.

For the first time in Japan, members of the CRB were appointed according to legal statute. The CRB was to comprise:

1. A specialist from medicine or medical care
2. Either a lawyer or bioethicist (with an understanding of respect for human rights)
3. A layperson

Bioethicists and lawyers were pigeonholed together and by including the requirement of an "understanding of respect for human rights," the government intended that these individuals would also serve as patient advocates. Furthermore, there was an ongoing confusion about what the government's understanding of "a layperson." At the time, we (the administrative office of the CRB) sought a layperson committee member in order to create an institutional review board in accordance with the law, but upon sending the resumes of candidates to the MHLW, they would inevitably deem some of the candidates "inappropriate."

My search for layperson committee members yielded individuals as diverse as a professor emeritus, a retired employee of a pharmaceutical company, a principal of elementary or junior high school, a Buddhist monk, and a homemaker.

Some members of the MHLW argued that the professor emeritus had a conflict of interest with this particular organization (personal communication). They also suggested that a person who had retired from working at a pharmaceutical company could be considered to be medical personnel (personal communication). Their opinions on these matters seemed to vary each time our committee's officer inquired. Some argued that even a homemaker could be considered a specialist in the field of bioethics, if this particular individual were a member of the Japan Association for Bioethics. Thankfully, the Buddhist monk was never deemed "inappropriate."

Nonetheless, it might be argued that the Buddhist monk was in fact the most questionable person to act as a lay member Within Buddhism, there are various sects, each of which may have different stances on medical research. If a Buddhist monk is acceptable, then what about a Catholic priest? If a research proposal for embryonic stem cell is presented, would a Catholic priest not object to this? What would this Catholic priest say about research studies that use aborted fetuses?

In a multiethnic nation such as the USA, a history fraught with racial discrimination and strong religious opposition gave rise to the need for the ethics review system, including the inclusion of lay members. Importing this system with the simple objective to meet international standards (or, perhaps Western standards) creates operational problems, particularly on-site.

Furthermore, the format of ethics committee member composition of Japan's CRB is similar to that of Western nations. However, if an empirical study were conducted to compare the content being reviewed by these boards, some surprising conclusions might emerge.

8.4 Scientific Misconduct in Research: Cultural Perspectives on Criteria for Authorship

A researcher's competence in the field of biology has come to be judged by criteria including the number of publications, the impact factors (IFs) of the journals in which he or she publishes, and the number of times their papers are cited by others. The December 2018 version of the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (by the International Committee of Medical Journal Editors: ICMJE)" clearly defines the criteria that one should fulfill to be considered an author of a paper.

This issue is complicated by cultural differences [5]. Fetters and Elwyn compared the numbers of authors per original article by Japanese and non-Japanese research groups in two qualitatively similar medical journals (*Circulation Research* [IF 11.6, 2015] and *Japanese Circulation Research* [IF 4.1, 2015]) [6]. In each of 3 years, they noted that 2–3 more Japanese authors were included per original article published in *Japanese Circulation Research* than in *Circulation Research*. They attributed this difference to cultural differences in crediting authorship, highlighting the Japanese group-ethics, the role of professors in conducting research, and the funding system. They concluded that "the movement to credit only those who deserve authorship is noble, though the assessment of legitimate authorship is a cultural, not a scientific judgment [6]"

The Japanese group-ethic is certainly one cultural perspective. Although ICMJE stipulate the definition of authorship, cultural norms also play a part.

8.5 Conflict of Interest in a Society Supported by Fiduciary Relationships

Although the concept of conflict of interest (COI) overlaps between countries, the practice varies widely. Japan's governmental "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (MEXT, MHWL) requires researchers to (1) ensure transparency, (2) include COIs in the protocol, and (3) explain COIs to participants. The Question and Answer section of these guidelines is also fairly

simple. Only the Clinical Research Act (CRA) has a detailed discussion about COIs. In other words, research studies not under the CRA are monitored differently, usually according to institutional discretion.

Perceptions of COIs may differ, for example, between the USA and Japan, as the USA comprises a society rooted in contractual agreements, whereas Japanese society is based upon by fiduciary relationships. Social perception of COIs may also reflect whether a society is biased toward fiduciary relationships or contractual agreements.

An example of this is material transfer agreements (MTAs). MTAs are mandatory for all international collaborative studies conducted today. While Japan is not exempt from these agreements, I suspect that few deans in Japan actually read MTAs before signing them. Very few domestic studies in Japan *formally* require them. They do not need MTAs so long as the parties are in a fiduciary relationships. Written documents (MTAs) therefore do not have priority.

These apparent differences give rise to the question about whether or not COI guidelines should be tailored to the culture, society, and healthcare system in which they take place. Should every institutions policy stipulate "the percentage of option stock or amount of money received from an industrial sponsor," or rather demand that researchers "stay within a range accepted by social norms?" Japan should develop a set of guidelines considered internationally acceptable while still being suitable for Japanese society and culture. In this way, the systems in place used to monitor COIs represents an excellent model for comparing cultural and social structures [7].

8.6 An Addendum: Hospital Ethics Committee and Clinical Ethics Consultation

8.6.1 Clinical Ethics Consultation

In addition to institutional review boards (research ethics committees), Japan also imported the Hospital Ethics Committee system and clinical ethics consultation system. A similar format to that used in the USA was established, while embodying different values in the Japanese context.

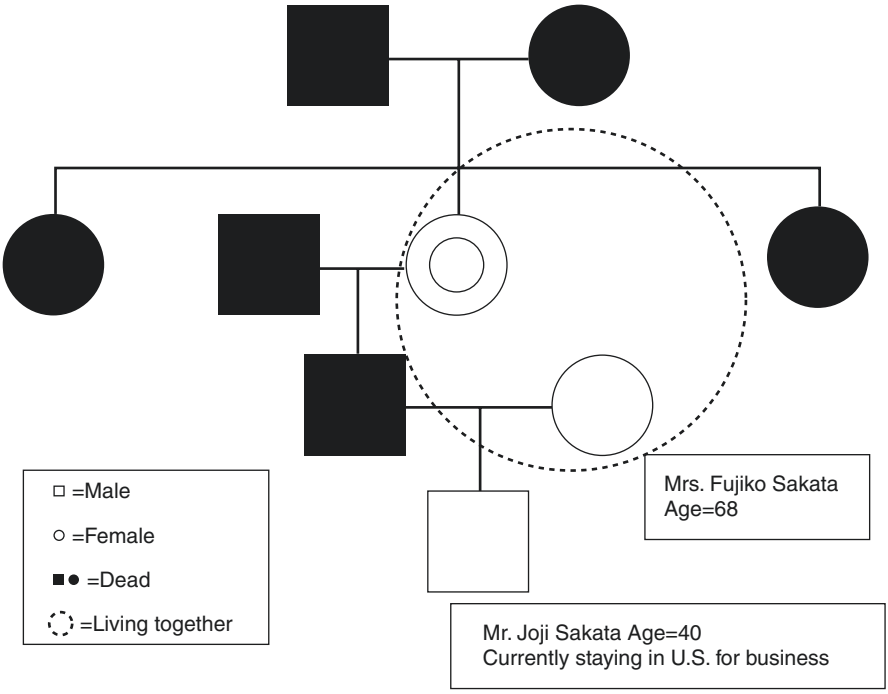
A study comparing the USA and Japan's Clinical Ethics Consultation [8], employing the exact same setting of a decision-making proxy for a patient with Alzheimer's disease, found that the content of advice differed by country. Differences were identified in recommendation and assessment between the American and Japanese participants. In selecting a surrogate, the American participants chose to contact the grandson (legally the most clearly designated person) before designating the daughter-in-law as the surrogate decision-maker. They made an effort to discern the patient's preferences and thereby obtain a suitable surrogate. In contrast, the Japanese experts assumed that the daughter-in-law (a more distant family member, but one who lived nearby) was the surrogate and asked her opinions on the matter, with the aim to obtain a best interest judgment.

Case (from Nagao et al. [8])

Name and age	Mrs. Mineko Sakata. Age = 92 SEX: Female
Diagnosis	Late-onset Alzheimer's disease.
Chief complaints	disturbance of consciousness, cognitive impairment, and dysphagia

The patient began to exhibit impairment of memory and orientation in 1998 and has been progressing ever since. Her family first brought her to our hospital in July 2000 when they discovered she was wandering about aimlessly and screaming in the middle of the night (ambulatory automatism). She was diagnosed with late-onset Alzheimer's disease.… The patient's family admitted her to X Elderly Care Facility in October 2005. While the patient was at the X Facility, she remained drowsy throughout the day and night.…. The patient could not chew or swallow, which made oral feeding difficult. In July 2006, the patient was transferred to our hospital. Our staff has tried to tube feed her via a nasal gastric tube; but she persistently removes the tube. The patient is currently physically stable and is not considered to be at the end-of-life stage. As a result, we recommended a gastrostomy (percutaneous endoscopic gastrostomy) for total enteral nutrition.

Mrs. Fujiko Sakata, the patient's daughter-in-law, has expressed that she would not want any other medical treatments if the patient were unable to eat. The patient also has a grandson whose name is Joji, Mrs. Fujiko Sakata's son. His opinion is that a gastrostomy would be allowed if it can prevent his grandmother from dying of starvation. Joji is currently in the USA since he has worked there for a long period of time.



8.6.2 *University of Tokyo Model: Patient Relations and Clinical Ethics Center (PRCEC)*

The structure of clinical ethics consultation (CEC) varies. After having observed many forms of CECs in other countries, I developed a unique CEC model for the University of Tokyo Hospital (1200 beds) [9].

The most prominent characteristic of my model is the combination of the patient complaint window with the CEC window. When a case is brought to the Center by a patient or hospital staff member, a nurse with extensive clinical experience and training in medical ethics serves as a gatekeeper and directs the case either to the complaints team or the ethics consultation team. The complaints team is made up of two nurses and three administrative staff members. If the case is assigned to the ethics consultation team, it is initially handled by the Center's vice director, a physician. He or she collects information and responses when the case requires an urgent response or, conversely, is relatively simple. Cases involving complex problems are handled by a CEC team composed of nurses, ethicists, and legal scholars from outside the medical school. Thus, the Center decides on a case-by-case basis whether to use an individual consultant or a team for ethics consultations. More complicated cases and those related to hospital policy are brought to the formal Hospital Ethics Committee.

So far, the Center handles approximately 2500 cases annually, among them about 5.0% were CECs.

The integration of CEC to handle patient complaints has relevant implications. First, this model ensures that patients and family members have free access to CEC services. At the PRCEC, about 25% of CEC services are used by patients or their families, indicating that this model is efficiently able to identify patient concerns (Fig. 8.3). Patients need not to determine the appropriate office to visit when they need advice or support. Furthermore, patients and family members must be able to, on their own, understand which problems are "ethical." Many patients and family members may not know what defines an ethical issue. This may be one reason why, although CEC services are available to patients and their families in the USA, use of these services remains low. The University of Tokyo model provides easy patient access to the relevant services, which reduces the burden of selecting the appropriate window.

The second implication of integrating CEC services with patient complaints is that it makes it easy to identify "ethical" issues within patient complaints brought to the office. A study conducted in the USA found that patient complaints covered a broad range of issues including communication problems, conflicts between patients and medical practitioners over treatment and care, and issues related to rights, such as confidentiality and informed consent. Some of these may be ethical issues, and in some cases, it may be more appropriate to conduct a CEC rather than treat them as

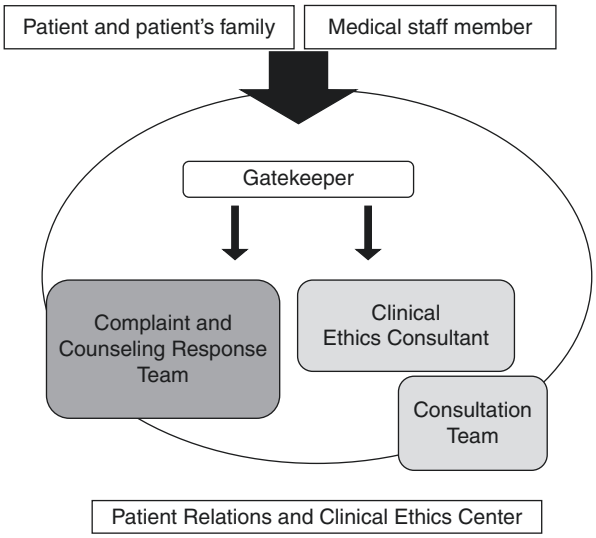


Fig. 8.3 Organization flow of PRCEC

mere complaints. In the USA, the Patient Advocacy Office is distinct from the Hospital Ethics Committee (HEC) or other offices that provide CEC services. Similarly, the Patient Advice and Liaison Service in the United Kingdom is separate from the division that provides CEC services. The PRCEC handles at least as many cases as USA hospitals of the same size, which provides some evidence of the efficacy of this model to identify ethical problems. The University of Tokyo model was presented at an international CEC conference and was well received. I hope that others involved in CEC systems would seek to develop more effective and appropriate frameworks that are in line with regional and institutional settings.

References

1. Slingsby BT, Nagao N, Akabayashi A. Administrative legislation in Japan: guidelines on scientific and ethical standards. Cambridge Q Healthcare Ethics. 2004;13:245–53.
2. Akabayashi A, Slingsby BT, Nagao N, Kai I, Sato H. An eight-year follow-up national study of medical school and general hospital ethics committees in Japan. BMC Med Ethics. 2007;8:8.
3. Akabayashi A, Nakazawa E, Akabayashi A. Implementation of Japan's first clinical research regulatory law: background, overview, and challenges. HEC Forum. 2019;31(4):283–94. https://doi.org/10.1007/s10730-019-09379-3.
4. Lancet Editors. Retraction--Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. Lancet. 2013;382(9895):843. https://doi.org/10.1016/S0140-6736(13)61847-4.
5. Akabayashi A. Misrepresenting research. In: Thomasma DC, Kushner T, editors. Ward ethics. New York: Cambridge University Press; 2001. p. 249–51.

6. Fetters MD, Elwyn TS. Authorship. Assessment of authorship depends on culture. BMJ. 1997;315(7110):747.
7. Akabayashi A, Slingsby BT, Takimoto Y. Conflict of interests: a Japanese perspective. Cambridge Q Healthcare Ethics. 2005;14:277–80.
8. Nagao N, et al. Clinical ethics consultation: examining how American and Japanese experts analyze an Alzheimer's case. BMC Med Ethics. 2008;9:2.
9. Takimoto Y, Akabayashi A. Clinical ethics consultation in Japan: The University of Tokyo model. Asian Bioeth Rev. 2011;3(3):283–92.