Administrative Legislation in Japan: Guidelines on Scientific and Ethical Standards

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Introduction

In the past few years, a second phase of biomedical ethics in Japan has begun to surface with a succession of governmental guidelines and laws regulating biomedical technology.[1] Although this rush of guidelines exemplifies a heightened awareness concerning ethical standards for healthcare research, it also invites several practical, political, and procedural problems.

In this report, we first provide an explanation of each of the main ministries involved with the drafting and implementation of these guidelines. Next, we present a table of the major guidelines and laws passed during the last two decades, describe the classification and legal binding power of governmental guidelines, and briefly explain the infrastructure of ethics committees in Japan. We then explore several shortcomings common among recent governmental guidelines. In particular, we highlight five possible limitations, including a lack of set standards for ethical reviews and the need for specific procedural instructions. Finally, we examine four specific guidelines in terms of social and historical necessity, political affiliation, content, and possible limitations specific to each guideline. In this analysis, we demonstrate how each guideline entails both common and specific limitations.

Description of Involved Ministries

Ministry of Education, Culture, Sports, Science, and Technology (MEXT)

The MEXT has the following three roles: (1) to reform the systems of education, culture enrichment, and science and technology; (2) to regulate those systems; and (3) to promote education, science and technology, culture, and sports. The bureau most involved with the drafting of ethical guidelines is the Science and Technology Policy Bureau, which is responsible for the planning and drafting of basic science and technology policies, including development programs and promotion of research evaluation.

Ministry of Health, Labor, and Welfare (MHLW)

The MHLW is dedicated to the protection and improvement of people's health and welfare. The MHLW serves as the authority for all matters of health and welfare, medical science, and technology. Medical institutions, including general hospitals, are under the jurisdiction of the MHLW (whereas academic

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institutions are under the jurisdiction of the MEXT). The Health Sciences Council of the MHLW has been active in the recent drafting of scientific and ethical guidelines.

Ministry of Economy, Trade, and Industry (METI)

The METI is responsible for all policies covering the nation's various industries, sources of energy, and foreign trade (except agricultural products and foods). The Commerce and Information Policy Bureau and the Industrial Science, Technology Policy, and Environmental Bureau are the two bureaus that have been most involved with discussions on scientific and ethical guidelines (e.g., industrial patents).

Overview of Guidelines and Laws

Table 1 lists the guidelines and laws (1989–2003) relevant to biomedical research and medical treatment. The Ministry of Health and Welfare (MHW), presently the MHLW, created the original Guideline for Good Clinical Practice (GCP) as a circular in 1989 to regulate clinical drug trials. The GCP was amended as a ministerial ordinance in 1997, along with the Pharmaceutical Affairs Law (1996), to harmonize domestic regulations of pharmaceutical testing with those in the United States and the European Union.[2] The new GCP lies in accordance with the GCP issued by the International Conference on Harmonization (ICH-GCP), which provides a unified standard for the United States, the European Union, and Japan.

Since 2000, five guidelines have been created, one has been amended, and one is currently being laid out. This highlights a succession of statutory measures over the past three years. Among these seven guidelines, the Ethical Guideline for Human Genome and Gene Analysis Research (2001) is the result of a collaborative effort by three ministries. The MEXT and the MHLW also collaboratively drafted the Ethical Guideline for Epidemiological Research (2002) and Guideline for Clinical Research on Gene Therapy (2002). The remaining four guidelines were either drafted or are currently being drafted by the MEXT or the MHLW.

Guidelines: Statutory Instruments

Japan's governmental scientific and ethical guidelines are classified as administrative legislation (*gyouseirippou*) and not as law (see Figure 1). In our interpretation, administrative legislation consists of statutory orders (*houkimeirei*) and administrative regulation (*gyouseikisoku*). The former includes, but is not restricted to, ministerial ordinances (*shourei*) and government ordinances (*seirei*). Although these apply to civil rights and duty, the latter includes notifications (*kokuji*), circulars (*tsuutatsu*), and other documents not concerning civil rights and duty. For example, the original GCP (1989) was a circular (*tsuutatsu*), whereas the new GCP (1997) is based on the amended Pharmaceutical Affairs Law (1996) and is classified as a ministerial ordinance (*shourei*). In contrast, the remaining guidelines listed in Table 1 are formally classified as ministerial notifications (*kokuji*).

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Table 1. Recent guidelines on scientific and ethical standards

Year	Administrative legislation	Affiliated ministry(s)*	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**
2001	Ethical Guideline for Human Genome and Gene Analysis Research	MHLW, MEXT, METI	Notification
2001	Guideline for Derivation and Utilization of Human Embryonic Stem Cells	MEXT	Notification**
2001	Guideline for the Handling of Human Embryos for Research	MEXT	Notification**
2002	Ethical Guideline for Epidemiological Research	MEXT, MHLW	Notification
2002	Guideline for Clinical Research on Gene Therapy (amended)	MEXT, MHLW	Notification
2003	Privacy Protection Law		Law
2003	Guideline for Clinical Research	MHLW	Notification
Pending	Guideline for Clinical Research Using Human Stem Cells	MHLW	Undecided

*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.

**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).

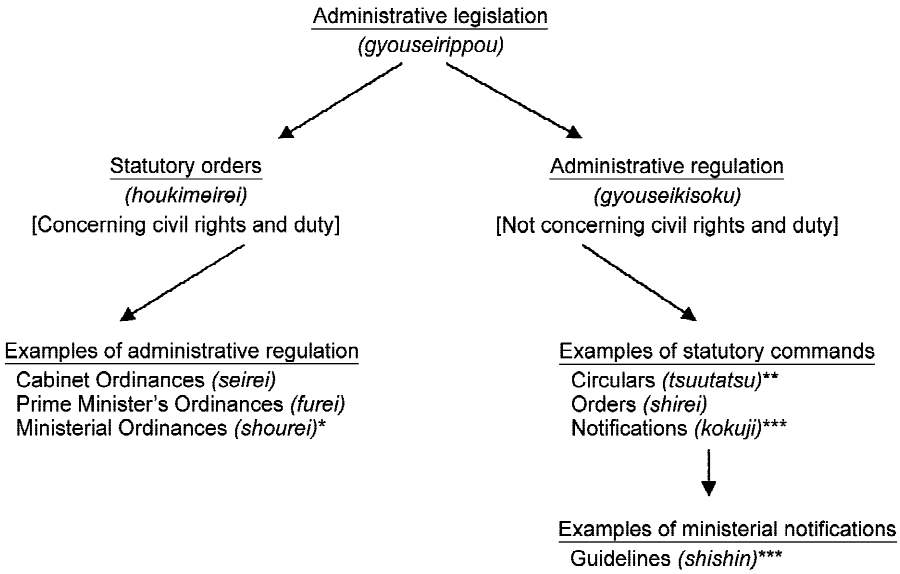

Figure 1. Statutory classification of guidelines (the authors' interpretation). *"The New Guideline for Good Clinical Practice" is a ministerial ordinance. **"The Original Guideline for Good Clinical Practice" was a circular issued by the Ministry of Health and Welfare, the Former Ministry of Health, Labour, and Welfare. ***All other guidelines are classified as ministerial notifications.

Ethics Committees in Japan

Although the Japanese term for ethics committees (*rinri-iinkai*) has been translated as institutional review board (IRB),[3] the infrastructure of ethics committees in Japan differs from that in the United States. There are two types of committees in Japan: (1) *chiken-shinsa-iinkai*, a review and monitoring committee (RMC) for drug clinical trials; and (2) *rinri-iinkai*, an ethics committee. RMCs review only drug clinical-trial protocols and monitor those trials; they are regulated by the MHLW and function in accordance with the ICH-GCP. Likewise, researchers of drug clinical trials are required by the new GCP to receive approval from an RMC. Conversely, an ethics committee is a self-governing body established by each institution and falls under the jurisdiction of neither the MHLW nor the MEXT. Ethics committees commonly review protocols from researchers affiliated with medical schools and general hospitals and also deal with hospital affairs, including hospital policymaking and clinical ethics consultation. In light of these disparities between RMCs and ethics committees, the English translation "institutional review board" is misleading in that the infrastructure and role of ethics committees in Japan fundamentally differ from IRBs in the United States. Although we noted that ethics committees are not under the jurisdiction of ministries, the guidelines set around 2000 strongly recommend that institution heads establish ethics committees.

Common Limitations among the Guidelines

The governmental guidelines, although capable of ensuring a high level of ethical and scientific standards for carrying out research projects, have several

possible limitations. One consistent limitation pertains to the issue of no set standards for the process of ethical review. None of the guidelines provide procedural details concerning the evaluation of a submitted study and standards of that evaluation. Given that standards may fluctuate among studies depending on methodology, samples, or subjects, further specification is needed to ensure a consistently high level of review. An additional problem is the entrusting of perfunctory procedures (e.g., the public release of information) to the discretion of ethics committees and/or individual researchers. The public release of information is intended to act as a double check and to ensure social accountability. Yet, without set standards and the proper release of information, half measures may be deemed as qualified standards, causing risks of social accountability, ethical obligation, and legal liabilities.

Another major issue is the lack of a central regulating body for local ethics committees. The lineup of guidelines has shifted the mainstay of responsibility to local institutional ethics committees. Yet, current local ethics committees have problems with infrastructure, management, and the recruiting of competent members. For each institution, deciding precisely how to run the committee efficiently and effectively is a persistent problem. For instance, the lack of set standards of organization for ethics committees leads to an inconsistent level of review between institutions. Without a central regulating body, insufficient evaluation may lead to approval of unethical practices and, eventually, procedural loopholes may be used intentionally.

A further problem is that the presence of several guidelines, although intended to safeguard against ethical risks, has caused difficulty and confusion for researchers. For instance, certain studies (e.g., epidemiological studies with human genome analysis) fall under both the Guideline for Human Genome and Gene Analysis Research (2001) and the Ethical Guideline for Epidemiological Research (2002). The former requires researchers to obtain written informed consent from all participants and to submit an annual written report; it also requires ethics committees to have at least two external members (preferably, more than half of an ethics committee). In contrast, the Ethical Guideline for Epidemiological Research addresses studies that do not require written informed consent, leaves the period for submitting a written report up to the discretion of the researcher, and only mentions that an ethics committee should have an external member(s). These disparities not only confuse researchers but also leave room for researchers to choose the easier route and circumvent a strict review process.

Another question that deserves attention is why are there so many guidelines and so few laws. Numerous guidelines have been published during the last three years, but only two laws concerning healthcare research have concurrently been passed (see Table 1). Whereas a law has definite binding power and can be strictly enforced, administrative legislation, as in the case of guidelines, has relatively less legal binding power. Nonetheless, governmental guidelines have significantly more binding power than guidelines published by academic societies or professional organizations such as the Japan Medical Association or the Japan Society of Obstetrics and Gynecology.

In sum, we believe the following five shortcomings require additional attention: the lack of set standards for ethical reviews, the necessity of a central regulating body for local ethics committees, the need for specific procedural instructions, possible inconsistencies between guidelines, and the regulatory limitations of partial binding power.

Four Representative Guidelines

The following discussion describes four guidelines in terms of (a) social and practical necessity, (b) administrative bodies involved, (c) content and purpose, and (d) possible limitations specific to each guideline.

Ethical Guideline for Human Genome and Gene Analysis Research[4]

Social and practical necessity. Human genome research and gene analysis involves many ethical concerns. The need for strict standards has been expressed by both UNESCO's Universal Declaration on the Human Genome and Human Rights[5] and the Basic Principles of Human Genome Research[6] developed by the Ethics Committee of the MEXT Council for Science and Technology.

Ministrative bodies. The MEXT, MHLW, and METI collaboratively drafted the guideline.

Contents and purpose. Chapter 1 defines seven basic principles including human dignity, confidentiality of personal information, and the priority of individuals' human rights over that of scientific or social benefits. Chapter 2 lays out the responsibilities of researchers, including the head of the research institution, the chief researcher, the personal information manager, and the ethics review committee. Chapter 3 attends to informed consent, disclosure of genetic information, and genetic counseling. Chapter 4 describes specific methods for the handling of samples.

Possible limitations. This guideline and its details attend to the "procedural minutes" in general but do not provide actual instructions for carrying out ethical and effective study and review. Although all facilities that offer specimens and samples are required to have an institutional ethics committee, small-scale cooperative facilities often face financial and administrative difficulties in running such committees. Also, the guideline lists several subsidiary rules concerning informed consent documents, but it remains unclear how to conduct proper informed consent under actual circumstances. Additionally, there is no outline for the process of genetic counseling even though the necessity of genetic counseling is stated. Monitoring is consigned to institution heads, which invites an almost unrealistic administrative burden. Finally, instructions for handling of human materials collected prior to the publication of this guideline are noted but lack clarity.

Ethical Guideline for Epidemiological Research[7]

Social and practical necessity. The collection of data in epidemiological studies often involves the risks of infringement of individual human rights and emerging of privacy protection. In response to the public's heightened awareness concerning the issue of privacy protection, the amended Privacy Protection Law (2003) aims to better protect individual rights. This law, although comprehensive, is not specific enough to attend to the risks involved with epidemiological research.

Ministrative bodies. The MHLW and MEXT are the authorities for this guideline.

Contents and purpose. The guideline provides ethical standards for designing, conducting, recording, and reporting epidemiological research that involves human subjects. It defines all terms concerned with epidemiological research, including "informed consent" and "ethics committee." The guideline stresses the protection of privacy and personal information and the priority of individuals' human rights over that of scientific or social benefits.

Possible limitations. Studies that include medical treatment, which constitute a major part of clinical epidemiological research, are excluded from the scope of this guideline. And although the guideline addresses studies that do not require individual informed consent and stresses the public release of information and the assurance of subjects' rights to decline participation in these cases, it is insufficient in detail as to how to carry out these ideals. Finally, the guideline addresses neither epidemiological gene analysis research nor refers to the Guideline for Human Genome and Gene Analysis Research.

Guideline for Derivation and Utilization of Human Embryonic Stem (hES) Cells[8]

Social and practical necessity. Following the discovery of hES cells in 1998, Japanese researchers began to conduct similar projects. Soon thereafter, a committee for hES cell research was established and the Bioethics Committee of the Cabinet's Science and Technology Council set up the Advisory Council for Human ES Cell Research.

Ministrative bodies. This guideline is under the auspices of the MEXT.

Contents and purpose. The guideline defines (1) standards for the derivation of hES cells, including requirements for human embryo use, (2) requirements for distribution of hES cells, (3) criteria for a deriving institution, (4) instructions on how to apply for approval through an institution's research ethics committee, and (5) donation of human fertilized embryos, including requirements for utilization and informed consent procedures. Each procedural step (derivation, distribution, utilization) requires a separate review. Each review process also consists of a double review aimed to ensure a high level of surveillance and regulation. The first review is performed by a researcher's institutional ethics committee and, on approval, the senior researcher applies for official approval to the MEXT. The guideline also spells out the penalties for breaking regulation (e.g., publication of researcher's name).

Possible limitations. The specific roles of each committee of the two-step review are unclear. So we have to ask: Without specific roles, is there meaning in a two-step review? And finally, the guideline lacks any mention of patent rights (i.e., filing for patents).

Guideline for Clinical Research[9]

Social and practical necessity. Between 2000 and 2003, a series of five guidelines were published, all of which were specific to a certain field of research (i.e.,

epidemiology) or methodology (i.e., gene analysis). Nonetheless, the specificity of these guidelines has also resulted in the lack of a general and comprehensive guideline for clinical studies.

Ministrative bodies. Given that clinical research (e.g., the testing of new therapeutic methods, diagnostics, and sociocultural aspects of patient care) comprises several apparent ethical risks, the MHLW drafted a comprehensive guideline for clinical research.

Contents and purpose. The guideline begins by defining all specific terms concerned with clinical research (e.g., subjects, researchers, chief researcher, informed consent, research institution, ethics committee). It then lays out the responsibilities of researchers including the institution head, the chief researcher, and the ethics committee. The guideline also specifies the parameters and methodology of informed consent, disclosure, and the protection of personal information.

Possible limitations. Because the guideline aims to fill in the gaps left by other guidelines, it inherently lacks any specification. It is abstract and does not offer practical guidance to researchers, and its scope is unclear in terms of both field and methodology.

Conclusion

According to the National Science and Technology Basic Plan, the Japanese government in 1995 and 2000 expanded their budget for healthcare research grants.[10] The drastic increase in healthcare research that resulted makes apparent the political and ethical need for scientific and ethical guidelines. Guidelines provide researchers with the standards and parameters necessary to carry out effective and ethical studies in an age of advancing technology. These guidelines, if enforced properly, could ensure a high level of ethical standards for designing, conducting, recording, and reporting scientific research projects.

However, as highlighted by this report, the guidelines have several shortcomings. To summarize, we found five possible limitations including: (1) the lack of set standards for ethical reviews, (2) the necessity of a central regulating body for local ethics committees, (3) the need for specific procedural instructions, (4) possible inconsistencies between guidelines, and (5) the regulatory limitations of partial binding power. Furthermore, our examination of four sample guidelines revealed several limitations specific to each guideline. The current situation, without a doubt, highlights the need for further discussion concerning these limitations and their implications on the ethical standards for scientific research and medical treatment. The rush of legislation on ethical standards for healthcare research exemplifies the active movement in Japan's political, public, and academic circles.

Notes

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