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Special Feature Article

New Ethical Guidelines for Psychiatric Research Involving Human Subjects

Yoshihiko IJIMA

Fujita Health University, Bioethics, School of Medicine

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Abstract

Researchers that conduct psychiatric studies, including genetic analysis studies, have to comply with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, as enforced in June 2021. New policies such as central ethical review, one protocol per a multi-center study, and e-consent have been introduced in this new regulatory framework. These new guidelines will increase the efficiency of research practice as long as the researchers conduct their research with a stronger sense of responsibility and adherence to the regulations.

Researchers have to ensure the privacy of study participants and consider the impact of the research results on society because of personally identifiable preparation and information in psychiatric studies. They must examine and determine the conditions for obtaining agreements with study participants, instructions on the use of genome information, the security requirements and management of personal information protection, the conditions for commercial use, among others, based on the laws and guidelines related to research ethics.

This paper clarifies the points needed for high-quality psychiatric research by overviewing the new guidelines and examining discussions of the ethical review committee of the Japanese Society of Psychiatry and Neurology (J. S. P. N.).

Keywords : psychiatric research, research ethics, ethical guidelines, central ethical review, e-consent

Introduction

The "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (hereinafter referred to as the "Guidelines for Medical and Health Research") were published on March 23, 2021 and came into effect on June 30 of the same year.⁷⁾ The "Ethical Guidelines for Medical Research Involving Human Subjects" and "Ethical Guidelines for Human Genome/Genetic Analysis Research" are to be reviewed every five years, and MEXT, MHLW, and METI, which have jurisdiction over the guidelines, have established a joint meeting⁸⁾ to review both guidelines and discuss how to further improve the system. As a result, it was decided that the two guidelines could be integrated, taking into consideration the points to be noted, and the Guidelines for Medical and Health Research were established (Figure).

Members of the Japanese Society of Psychiatry and Neurology (hereafter referred to as "the society") must conduct research in compliance with laws, regulations, and guidelines, including the Guidelines for Medical and Health Research, while referring to the "Code of Ethics for Clinical

Research"⁹⁾ established by the society in 1997.¹⁰⁾ The author has been dealing with ethical issues in psychiatric research as an external member of the Ethics Committee of this society since 2011. Based on this experience, the author would like to discuss the issues that members of this society should be particularly aware of when planning and conducting psychiatric research following the Guidelines for Medical and Health Research.

I. About the Ethics Committee of the Japanese Society of Psychiatry and Neurology

The society was an early leader in addressing issues related to research ethics. In 2009, the society established the Ethics Committee, which is the current committee, to review research projects initiated by or involving the society and improve the research ethics and literacy of society members by organizing symposia and education/training on research ethics at the annual conference (Table 1). In response to the rapidly changing regulations governing research, we have developed suggestions and guidelines on research ethics for

psychiatric research as needed. In March 2011, after the Great East Japan Earthquake, we issued an emergency statement on research and investigation in the areas affected by the earthquake.²⁾ In 2016, we published an addendum to the Code of Ethics for Clinical Research.¹⁰⁾ In the same year, in light of the importance of case reports, the "Guidelines for the Protection of Privacy in Medical Papers and Conference Presentations Including Case Reports" was formulated.¹¹⁾

The number of studies reviewed by the society's Ethics Committee is not necessarily large, with only a few per year, and there are many studies that are not covered by the Guidelines for Medical and Health Research, such as unscored questionnaires. On the other hand, there are cases in which "special consideration" is required when psychiatric patients are the subjects, and the Ethics Committee deliberates carefully.

II. Expanding Scope of Application of the Guidelines for Medical and Health Research

It is important for researchers to determine which laws and guidelines apply to them when designing and conducting research. The Guidelines for Medical and Health Research may be applied to research in the humanities and social sciences that involve human

subjects. For example, research using a drive simulator in medical-engineering collaboration, research using MR imaging in the field of educational development, and behavioral response research based on game theory in the field of economics may or may not be subject to the Guidelines for Medical and Health Research, depending on whether they fall under the definition of "medical science." Therefore, it is necessary to be careful. Research using only "samples and information that have established academic value, are widely used for research purposes, and are generally available" (e.g., samples provided by commercial biobanks) is not considered to be covered by these guidelines. However, it is advisable to check with the ethics review committee of your institution in advance to make a specific judgment.

So-called "case reports," which are reports of individual cases that are frequently presented at the society, do not constitute research and, in principle, are not subject to the Guidelines for Medical and Health Research. In view of the importance of case reports, the society has prepared and published guidelines.¹¹⁾ The guidelines require anonymization to protect the privacy of subjects of reports, and also require consent to be obtained whenever possible. In addition, the guidelines recommend obtaining opinions of ethics

review committees of institutions to which researchers belong if there is any doubt as to whether case reports constitute research.

III. Use of Cooperative Research Organizations in Registry Research

In the field of psychiatry, registry studies are sometimes conducted by collecting samples and information. In registry research, institutions that provide samples and information do not necessarily have the purpose or intention of conducting the research, and imposing various responsibilities on them as research institutions and researchers may result in excessive burdens. In cases where existing samples and information collected for the purpose of medical treatment are only provided to other research institutions, the provider can submit a notification to the head of the institution as "a person who only provides existing samples and information," depending on the degree of anonymization, so that the head of the institution can identify the provider, or by obtaining permission, the provider does not have to assume responsibilities as a researcher. However, it has also been clarified that even when new samples and information are obtained for research purposes, if the invasion is minor, the researcher may be removed from the research institution as a

"cooperating research institution" and not assume responsibilities as a researcher. Possible cases in which the "research collaborating institution" rule may be used include the provision of MR image data obtained for medical treatment purposes at a clinic near the research institution, or when a patient with a rare disease has his/her blood drawn for research purposes at a clinic located in an area away from the research institution and provides the blood to that institution.

When a clinic that is a member of the society provides samples to a research institution to diagnose a rare disease or only provides imaging data or medical information to cooperate in registry research, if the clinic provides the samples as a research collaborating institution or "a person who only provides existing samples and information," it is exempt from the system as a research institution. Since the revised Act on the Protection of Personal Information will be directly applied to academic research from FY2022 and treated as an "exception," a safety management system for personal information is required.

However, informed consent from research subjects must be obtained by "researchers" at the recipient institution, and when the recipient and research institutions are far apart, it may be reasonable to use

electromagnetic informed consent (e-consent), which will be discussed later. Principal investigators overseeing registry research should take advantage of the provisions for "cooperating research institutions" and "persons who only provide samples and information" to facilitate research.

IV. Conducting Multi-institutional Research - One Research One Protocol and Central Ethical Review

The Guidelines for Medical and Health Research define research conducted at multiple institutions based on a single research protocol as "multi-institutional collaborative research." In multi-institutional collaborative research, a principal investigator must be appointed from each of the participating institutions. The principal investigator of multi-institutional collaborative research must prepare a single research protocol after clarifying the roles of the principal investigator of each participating institution, and each researcher must conduct research based on the same protocol (one research protocol). Although in clinical trials to verify the safety and efficacy of drugs, etc., participating institutions usually conduct research based on a single research protocol, in the case of observational research, where the nature of the research is diverse, it may be conducted according to different

research protocols at different institutions. It will be necessary to conduct research based on a single research protocol in the future.

Under the Guidelines for Medical and Health Research, the principal investigator who presides over a multi-institutional collaborative research project must, in principle, apply to a single ethics review committee for review of the research protocol (central ethical review). Under the guidelines, the principal investigator should directly apply for review by an ethics review committee within or outside the research institution, without going through the head of the institution. After approval by the ethics review committee, the principal investigator and each principal investigator of the collaborating institution who received the review approval letter from the principal investigator will obtain permission to conduct the research from the heads of the respective research institutions. When applying for ethics review, the destination of the application is not limited to the ethics review committee of one's own institution. However, as the quality of ethics review committees has been pointed out to vary, some institutions require confirmation of the rules of the institution by the administrative office before applying for ethics review by an ethics review committee outside the

institution to which the researcher belongs. With the introduction of central ethical review, there is a trend toward charging for ethics review, and in an increasing number of cases, researchers, such as principal investigators, are required to include the review fee in their research expenses.

The Guidelines for Medical and Health Research do not preclude individual ethical review by each participating institution. The principal investigator will confirm with the principal investigator at each participating institution whether ethics review is required at his/her institution. If the ethics review committee that conducts the central review requires it, the principal investigator from the institution that approves the central review will compile the materials (which may differ depending on the ethics review committee) necessary for the review, such as the confirmation of institutional requirements, and submit them to the ethics review committee that conducts the review.

Central ethical review by a single ethics review committee could have been conducted under the previous guidelines for medical science, but there were many issues such as complicated procedures and excessive administrative burdens.³⁾ The Guidelines for Medical and Health Research introduce procedures similar

to those of the Clinical Trials Act, thereby reducing the administrative burden of central ethical review to a certain extent.

V. Registration of Research

The Guidelines for Medical and Health Research require all interventional research to be registered, and efforts must be made to register observational studies as well (obligation to make efforts). The Declaration of Helsinki,¹²⁾ an international code of research ethics, requires registration for research within the scope of the declaration, and in this respect, it can be evaluated as approaching international standards. The recommended registration destination is jRCT (Japan Registry of Clinical Trials),⁵⁾ a public database of the Ministry of Health, Labour and Welfare (MHLW), but UMIN-CTR,¹⁾ which has been used up to now, is also acceptable. It is optional for researchers to register their studies in public databases outside Japan.

It should be noted that study registration must be done before the start of the study. It is also necessary to register not only at the beginning, but also at the point of any change in the research content and at the end of the research. In multi-institutional collaborative research, the principal investigator can register the data centrally.

VI. Electromagnetic Informed Consent (e-consent)

There are no major changes in the Guidelines for Medical and Health Research regarding provisions for informed consent from research subjects, other than the new provision of electromagnetic informed consent (e-consent). The consent for participation in research is divided into "written consent," "appropriate consent," "oral consent plus documentation," and "disclosure of information plus guarantee of opportunity to refuse (opt-out procedure)," depending on the situation, according to the degree of risk and burden on the research participant (Table 2).

E-consent means that consent is obtained from the research subject through explanation in electromagnetically recorded text, etc. In particular, e-consent is used for non-face-to-face communication (e.g., videophone). In the case of non-face-to-face communication (including face-to-face communication by videophone, etc.), consent should not be obtained unless the research subject confirms that he/she has received and understood the explanation. E-consent is more applicable to observational studies such as registry research, rather than clinical trials in which patients visit the hospital for face-to-face explanations. In

the future, the enhancement of opt-in by e-consent will be important to promote the utilization of samples and information, and it is important to note that the pros and cons of providing samples and information for a fee and the nature of informed consent in the case of providing samples and information to commercial companies will be questioned.

In the implementation of non-face-to-face e-consent, it is important to ensure identification and interactivity. The method of identification must be appropriate and strong depending on the content and nature of the research. The research subjects should be given the opportunity to ask questions about the content of the explanation, these questions should be answered sufficiently, and the research subjects should be able to easily access the consent items, including the explanations provided in the regulations, even after consent is obtained. In particular, the relevant document should be delivered when requested by a research subject or other parties.

VII. Explanation of Research Results

Disclosure of the results of genetic analysis in the Ethical Guidelines for Human Genome/Genetic Analysis Research is now defined as "explanation of the results obtained from the

research" in the Guidelines for Medical and Health Research. This relates to the policy for returning information such as incidental findings and other information obtained incidentally through examination of individual research subjects, etc., rather than the results of the research itself (including cases in which the information is not returned), although the disclosure should be positive when it is beneficial to research subjects, depending on the nature of the examination results, etc., to be disclosed. On the other hand, if it is detrimental to the subject of the research, a careful response is desirable. The researcher should establish an explanation policy for the research that will be conducted, and disclose said policy to the research subjects, in accordance with the characteristics of the research plan, including: (i) the accuracy and certainty of the results, (ii) their importance to the health of the research subjects, and (iii) their impediments to appropriately conducting the research work.

Conclusion

The Guidelines for Medical and Health Research do not change the basic principles of the former guidelines, such as the "Basic Policy for Conducting Research," and researchers should basically continue to conduct their research as before. Under the

Guidelines for Medical and Health Research, researchers may apply for ethical review without going through the head of the research institution, so care must be taken not to start research without first obtaining permission to conduct it from the head of the institution based on the approval of the ethical review. Because of the increased responsibilities and duties of principal investigators and other researchers in conducting research, it is important to establish a research office to support the conducting of research in multi-institutional collaborative situations, and receive support from the clinical research support department of the institution to which the investigator belongs, if necessary. In registry research, it is possible to promote research by utilizing cooperating research institutions and e-consent regulations, and it is important for researchers at medical institutions. In order to operate successfully, it is also important for researchers at non-research medical institutions and private clinics to understand the Guidelines for Medical and Health Research.

In accordance with the revision of the Act on the Protection of Personal Information, the Guidelines for Medical and Health Research are scheduled to be revised and enforced in FY2022.⁶⁾ In November 2021, at the time of writing

this paper, a public comment period began for the "Partial Amendment to the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Summary)."⁴⁾

There are many factors that must be understood when conducting research, such as elaboration of exemptions from the Act on the Protection of Personal Information for academic research as exception provisions for each item, and it is necessary to catch up on information concerning the revisions.

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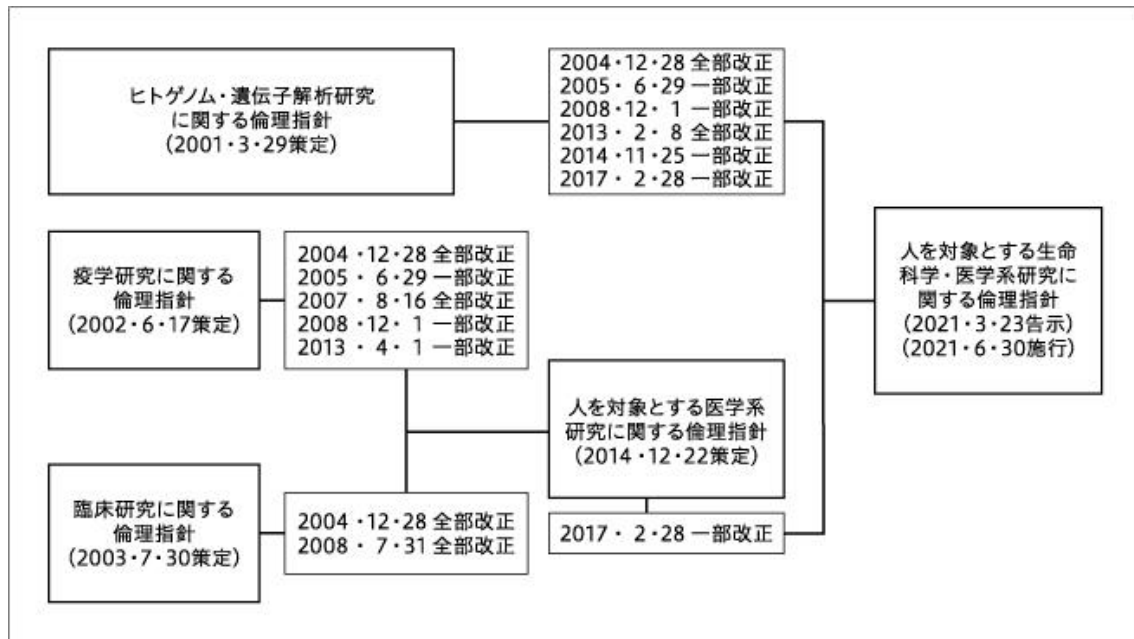


図 倫理指針統合の歴史

Figure. History of Ethical Guideline Integration

表 1 倫理委員会企画による本学会学術総会シンポジウム
テーマ

年	テーマ
2017	精神医学研究における倫理課題——個人情報保護法改正と倫理指針改定を受けて——
2018	精神医学研究の倫理——症例報告から大規模データ研究まで——
2019	症例報告における倫理的配慮——本人同意をめぐる課題——
2020	同意取得が困難な事例を対象とした症例報告や研究における問題点と課題
2021	倫理指針改正による多施設研究と試料・情報利用研究へのインパクト

Table 1. Themes of Symposiums at Annual Meetings of the Society Planned by the Ethics Committee

Year/Theme

2017

Clinical, Ethical, and Philosophical Perspectives on Psychiatric Research

2018

Ethics of Psychiatric Research: From Case Report to Registry Research

2019

Ethical Considerations in Case Reports - Issues Concerning Individual Consent

2020

Issues and Challenges in Case Reports and Research on Cases in which Consent is Difficult to Obtain

2021

Impact of Revised Ethical Guidelines on Multi-Center and/or Observational Studies

表2 インフォームド・コンセント

侵襲の有無	介入の有無	人試料採取	インフォームド・コンセント 手続き		
侵襲あり		文書による同意取得			
侵襲なし	介入 (+)		文書同意 or 口頭同意 + 記録		
	介入 (-)	新規	人体試料 (+)	文書同意 or 口頭同意 + 記録	
		人体試料 (-)	要配慮個人情報使用	文書同意 or 適切な同意 or 拒否機会保障 (オプトアウト)	
			要配慮個人情報不使用	文書同意 or 拒否機会保障 (オプトアウト)	
		既存	人体試料・情報	文書同意 or 匿名化 or 拒否機会保障 (オプトアウト)	

Table 2. Informed Consent

Invasive/Intervention/Human sample collection/Informed consent procedure

Invasive/Obtaining written consent

Non-invasive

Intervention (+)/Documented consent or oral consent + documentation

Intervention (-)

New

Human specimen (+)/Documented consent or Oral consent + Record

Human specimen (-)

Use of sensitive personal information/Documented consent or Appropriate consent or Guaranteed opportunity to refuse (opt-out)

No-use of sensitive personal information/Documented consent or Guarantee of opportunity to refuse (opt-out)

Existing/Human specimens, Information/Documented consent or Anonymization or Guaranteed opportunity to refuse (opt-out)