

General Comments

The Japan Addendum to the *Evaluation Instrument for Accreditation* (“*Evaluation Instrument*”) is intended for use by organizations in Japan seeking accreditation, by site visitors evaluating organizations in Japan, and by accredited organizations in the US that conduct or oversee research in Japan. This Addendum includes Standards and Elements where Japanese law, regulations, and guidelines require significant additional protections beyond those defined in the *Evaluation Instrument* and is intended to be used in conjunction with the *Evaluation Instrument*. The Addendum focuses on the laws most relevant to human research protection programs, including research ethics committees. However, it is not an exhaustive account of all requirements covering research involving human participants in Japan. The Addendum is based on a review of the following laws, policies, and guidance:

- Act on the Safety of Regenerative Medicine (2014)
- Clinical Trials Act (Act No. 16 of April 14, 2017)
- Ethical Guidelines for Medical and Health Research Involving Human Subjects (Provisional translation March 2015) (“Ethical Guidelines”)
- Pharmaceutical, Medical Devices, and Other Therapeutics Act (PMD Act 2014)
- Japan GCP
- GCP Ministerial Ordinance on the GCP MHLW Ordinance No. 9 dated January 22, 2016

When following GCP, organizations should ensure that all the requirements of ICH-GCP (E6) in the *Evaluation Instrument* are included in written materials.

This Addendum represents AAHRPP’s current understanding of additional requirements covering organizations conducting or reviewing research in Japan.

We appreciate questions, concerns, and suggestions to improve this document. Please email accreditation@ahrpp.org.

Domain I: Organization

Standard I-1: The Organization has a systematic and comprehensive Human Research Protection Program with appropriate leadership.

Element I.1.A. The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.

Written materials must include a definition of “research”:

- Medical and Health Research Involving Human Subjects means an activity involving human subjects (including specimens and information acquired from them) to be carried out for the purpose of

obtaining knowledge contributing to maintain and promote people's good health or to recover from injury and disease and improve quality of life for patients, through understanding the cause of diseases (including the frequency and distribution of various health-related incidents and factors affecting them) and their pathology and through improving measures to prevent injury and disease as well as diagnostic and treatment measures in medical care or through verifying those measures' validity. (Ethical Guidelines, Chapter 1, Part 2)

- Clinical Trial means research (including observational studies) to establish the efficacy or safety of drugs, medical devices, or cellular and tissue-based products. "Specified clinical trials" refers to interventional studies of unapproved or off-label medical products and on-label medical products sponsored by their manufactures or distributors. (Clinical Trials Act)
- Clinical Trial also refers to studies related to the approval of new medical products that are defined and conducted in accordance with the provisions of the Pharmaceuticals and Medical Devices Act in pursuit of new marketing applications. (Pharmaceutical Affairs Act)
- Regenerative Medical Products mean processed human cells intended to be used for the reconstruction, repair, or formation of structures in the human body; or for the treatment of disease; or for gene therapy. (Act on the Safety of Regenerative Medicine)

Research Subject means a person (including deceased individual) who corresponds to any of the following descriptions:

- An individual on whom research is implemented (including an individual asked to be enrolled in the research); or
- An individual from whom existing specimen or information had arisen.

(Ethical Guidelines, Chapter 1, Part 2)

Element I.1.B. The Organization delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program.

Written materials describe the responsibilities of the chief executive officer or delegate (Ethical Guidelines, Chapter 2, Part 6):

- Overall supervision of research
 - The chief executive of research implementing entity shall exercise necessary supervision over the research he/she approved for implementing in order that it shall be carried out appropriately and shall take ultimate responsibility for it.
 - The chief executive of research implementing entity shall ensure that those involved in the research work carry out the research with due respect to the life, health, and human rights of the research subjects.
 - The chief executive of research implementing entity shall not disclose, without any justifiable reason, information obtained during the duties related to the research. The same shall

- apply even after he/she has ceased to be engaged in the duties.
- When entrusting a part of research work, the chief executive of research implementing entity shall enter into a written agreement for matters the contractor(s) shall comply with and shall exercise necessary and appropriate supervision of the contractor(s).
 - Arrangement, etc. of systems and procedures for implementation of research
 - The chief executive of research implementing entity shall arrange systems and procedures necessary for the appropriate implementation of research.
 - When a research subject has incurred any injury related to the research carried out by the research implementing entity, the chief executive of the research implementing entity shall ensure that necessary measures are taken appropriately, such as compensation for the research-related injury.
 - The chief executive of research implementing entity shall ensure that information concerning its research, including results of the research, shall be made public appropriately.
 - The chief executive of research implementing entity himself/herself shall, as necessary, verify and review whether the research carried out by the research implementing entity is complying with these Guidelines and shall take appropriate measures based on the results of such verification and reviews.
 - The chief executive of research implementing entity shall take measures to ensure that investigators, etc. of the research implementing entity shall receive education and training related to the ethics of research, as well as knowledge and skills necessary to carry out the research. The chief executive of research implementing entity himself/herself shall also receive such education and training.
 - The chief executive of research implementing entity may delegate the authority and duties set forth in these Guidelines to appropriate individual(s) who belong to the research implementing entity in accordance with the procedures established at the research implementing entity.
 - Approval of research
 - When the chief executive of research implementing entity is asked by a principal investigator for approval for any implementation of research or revision of the approved research protocol, the said chief executive shall submit the matter to the ethical review committee for deliberation and make a decision on relevant measures, such as approval, disapproval, etc., to the matter with due respect to opinions presented by the ethical review committee.
 - When the chief executive of research implementing entity has received any report from a principal investigator or other investigators, etc. concerning facts or information deemed to affect the propriety of the continuance of research, the said

- chief executive, as necessary, shall submit the matter to the ethical review committee for deliberation and, with due respect to opinions presented by the ethical review committee, take appropriate countermeasures promptly such as suspension of the research and examination of the cause.
- The chief executive of research implementing entity shall provide cooperation with the investigation carried out by relevant ethical review committee.
 - When the chief executive of research implementing entity has received any report concerning the fact or information that appropriateness of implementing the research or reliability of results of the research is, or might be, impaired, the said chief executive shall take relevant measures promptly.
 - When the chief executive of research implementing entity has received any report from a principal investigator that research has finished, the said chief executive shall report necessary matters to the ethical review committee which made reviews on the said research.
- Report to the Minister(s)
 - When the chief executive of research implementing entity becomes aware that any research which the entity is implementing or implemented previously is not complying with these Guidelines, the said chief executive shall promptly submit the matter to the ethical review committee for deliberation and take relevant measures as well as, if such noncompliance is serious, shall report to the Minister of Health, Labour and Welfare (if the research implementing entity is a college/university and the like, to the Minister of Health, Labour and Welfare and the Minister of Education, Culture, Sports, Science and Technology; hereinafter referred to the “Minister(s)”) concerning the status and results of such countermeasures and make the said status and results public.
 - The chief executive of research implementing entity shall provide cooperation with the inspection carried out by the Minister(s) or entity(s) entrusted with the duties by the Minister(s) to confirm that the research carried out by the research implementing entity is complying with these Guidelines.
 - When any unexpected serious adverse event occurs in implementing of the research which involves invasiveness (not including minor invasiveness) and intervention and if the said unexpected serious adverse event may be in direct consequence of the research, the chief executive of the research implementing entity shall report to the Minister of Health, Labour and Welfare concerning the status and results of countermeasures pursuant to the provisions of Section 3 (2) above and make the said status and results of such countermeasures public.

Written materials describe the responsibilities of the chief executive officer or delegate (Ethical Guidelines, Chapter 3, Part 7):

- The chief executive may grant approval prior to deliberation by relevant ethical review committee, however, when it is considered necessary to implement the research urgently in order to prevent public health-related harm from occurring or spreading. In this case, the said chief executive shall submit the matter to the ethical review committee for deliberation without delay after giving approval, and if the ethical review committee forms an opinion that the research shall be suspended or terminated or that revision shall be made in the research protocol, the said chief executive shall respect such opinions and take appropriate measures, such as ordering the principal investigator to suspend or terminate the research or getting the research protocol revised. (Ethical Guidelines, Chapter 3, Part 7)
- The chief executive of the research implementing entity shall not approve the implementation of the research if the ethical review committee has considered it inappropriate.

Standard I-4: The Organization responds to the concerns of research participants.

Element I.4.B. The Organization conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement.

The organization shall make public in the Ethical Review Committee Reporting System:

- The organization of and provisions for operating
- List of members of the committee
- The status of the committee's meetings held and a summary of the committee's reviews at least once a year. With respect to the summary of the committee's reviews, however, any of the contents may be omitted from such publication, when the committee considers it shall be confidential in order to protect human rights of the research subject, etc. and other individuals concerned or rights and interests of the investigator, etc. and other entity concerned.

(Ethical Guidelines, Chapter 4, Part 10)

Standard I-7: The Organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

Element I.7.A. When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.

Interventional studies intended for marketing applications are overseen by the Pharmaceutical and Medical Devices Agency (PMDA).

- Written materials must describe the process to obtain an IND for research designed to support a marketing application for an investigational drug or device. (Pharmaceutical, Medical Devices, and Other Therapeutics Act)

Health research (e.g., observational studies, interventional studies human genome analysis) not intended to result in an application for marketing application are overseen by the Ministry of Health, Labor, and Welfare (MHLW).

- Written materials must describe the process to comply with MHLW requirements for health research. (Clinical Trials Act)

Regenerative medicine research is overseen by either MHLW, if research involves cells for which safety and efficacy have not been established, or by the PMDA. (Act on the Safety of Regenerative Medicine)

Standard I-9: The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization the rights and welfare of research participants are protected.

Written policies describe the process to apply to have multi-site review evaluated by a single IRB:

- The chief executive of research implementing entity may submit a matter to a single ethical review committee for deliberation to make a comprehensive review on the research protocol for the research to be conducted collaboratively with other research implementing entity(s).
(Ethical Guidelines, Chapter 7, Part 3(3))

Domain II: Institutional Review Board or Ethics Committee

Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.

Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.

Each ethics committee must have at least five members, including the following, at a minimum:

- Expert in natural science, such as a medicine and medical care professional (scientific areas)
- Expert in humanities and social sciences, such as a professional in ethics and law (nonscientific areas)
- A member who can provide opinions of the general public, including viewpoints of research subjects (general perspective of research participants)
- At least two members who do not belong to the organization to which the organizer of the committee belongs (unaffiliated members)
- Both male and female members

(Ethical Guidelines, Chapter 4, Part 11)

In addition:

- No EC has members who represent a single profession. (AAHRPP Element II.1.A.)
- The expert in natural science, the expert in humanities and social sciences, and the member who can provide opinions of the general public cannot concurrently hold status for other groups. (AAHRPP Element II.1.A.)

Element II.1.D. The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.

Written materials require that:

The chief executive of the research implementing entity who submitted the matter for which the ethical review committee makes deliberation shall not be present when deliberation and adoption of opinions are made at the committee's meeting. When it is necessary to do so in order to understand the details of deliberation made by the ethical review committee, however, the said chief executive may attend the meeting by obtaining the committee's consent. (Ethical Guidelines, Chapter 4, Part 11)

Standard II-2: The IRB or EC systematically evaluates each research protocol or plan to ensure the protection of participants.

Element II.2.A. The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by researchers or others who might have a conflict of interest regarding the studies.

The Ethical Guidelines shall not apply to research which corresponds to any of the following:

- Research carried out pursuant to the provisions of laws and ordinances;
- Research included in scope of the code of conduct set forth by laws and ordinances; or
- Research utilizing only the specimens and information listed in the following:
 - Specimens and information, the value of which has already been established academically, widely utilized in research, and generally available; and
 - Information which has already been anonymized unlinkably.

(Ethical Guidelines)

Element II.2.C. The IRB or EC has and follows written policies and procedures to conduct limited review by the IRB or EC, if such procedures are used.

Applicable only to organizations that are not required to follow US DHHS regulations. Organizations that do not follow US DHHS regulations do not need to address this in policies and procedures.

Element II.2.D. The IRB or EC has and follows written policies and procedures for conducting meetings by the convened IRB or EC.

At convened meetings, a quorum must be present to conduct business (Ethical Guidelines, Chapter 4, Part 11):

- A majority of IRB members must be present.
- At least one expert in natural science, such as a medicine and medical care professional.
- At least one expert in humanities and social sciences, such as a professional in ethics and law.
- A member who can provide opinions of the general public, including viewpoints of research subjects.
- At least two members who do not belong to the organization to which the organizer of the committee belongs and who is not part of the immediate family of a person who is affiliated with the organization.

Whenever possible, ethics committees should endeavor to have a unanimous vote.

Element II.2.F. The IRB or EC has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used.

Expedited review may be used under any of the following categories:

- Review of research to be conducted collaboratively with other research implementing entity(s), the entire scope of which has already been reviewed by the ethical review committee to which the collaborative research entity(s) submitted it for deliberation and opinions to indicate the appropriateness of such research have already been presented;
- Review of minor revisions of research protocols;

- Review of the research which does not involve any invasiveness and intervention; or
- Review of the research which involves minor invasiveness but does not involve any intervention.

(Ethical Guidelines, Chapter 4, part 10)

These categories replace those listed in the *Evaluation Instrument* when following Japanese law. When following Japanese law and other laws, such as US DHHS regulations, expedited review may only be used when it complies with the totality of applicable laws.

The Ethical Guidelines and other laws, regulations, or guidelines do not appear to allow organizations to stop conducting continuing review of research approved using the expedited procedure.

Element II.2.G. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.

Researchers must report unexpected serious adverse events (Ethical Guidelines, Chapter 1, Part 2 and Chapter 7, Part 17) including:

- A Serious Adverse Event is an event that
 - Results in death;
 - Is life-threatening;
 - Requires inpatient hospitalization or prolongation of existing hospitalization;
 - Results in persistent or significant disability or incapacity; or
 - Is a congenital anomaly or birth defect to offspring.
- Unexpected Serious Adverse Event is a Serious Adverse Event that is not consistent with the information in the research protocol, the document used for obtaining informed consent and so on, or not consistent with the severity described in such, even if there is any description about the event.

Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.

Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.

The required disclosures will be provided to each participant or a legally authorized representative in accordance with legal and regulatory requirements. Required disclosures include (Ethical Guidelines, Chapter 5, Part 12):

- A statement that the study involves research.
- The title of the research and the fact that approval of the chief executive of the research implementing entity has been given concerning its implementation.
- Names of the research implementing entity and the principal investigator (including names of the collaborative research

implementing entity(s) and principal investigators of such collaborative research implementing entity(s), when the research is conducted collaboratively with other research implementing entity(s)).

- Objectives and significance of the research.
- An explanation of the purposes of the research (including purpose of the utilization of specimens or information acquired from the research subject).
- Burdens to be caused on the research subjects and predictable risks and benefits.
- An explanation of the expected duration of the participant's participation.
- A description of the procedures to be followed.
- Identification of any procedures that are experimental.
- A description of any reasonably foreseeable risks or discomforts to the participant.
- A description of any benefits to the participant or to others, which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.
- An explanation as to whether compensation is available if injury occurs.
- When the research involves any invasiveness, if compensation is available when injury occurs, an explanation as to what it consists of or where further information may be obtained.
- An explanation as to whether any medical treatments are available if injury occurs.
- If medical treatments are available when injury occurs, an explanation as to what it consists of or where further information may be obtained.
- Handling of personal information, etc. (including process of anonymization, when anonymization is conducted).
- Means to make information on the research public.
- The fact that research subjects, etc. can request and obtain or read the research protocol and documents concerning method of the research, to the extent it does not interfere with the protection of personal information, etc. of other research subjects, etc. or the originality of the research, as well as the procedure to obtain or read such protocols and documents.
- An explanation of whom to contact for answers to pertinent questions about the research.
- Means for storage and disposal of specimens and information.
- Status of research-related conflicts of interest of the research implementing entity.
- When any significant finding concerning the subject's health or generic characteristics which may be inherited by his/her offspring, etc. may be obtained through implementing the research or

handling of the research results related to the research subject (including incidental findings).

- An explanation of whom to contact for answers to pertinent questions about the research participants' rights.
- An explanation of whom to contact in the event of a research-related injury to the participant.
- Contact information for the research team for questions, concerns, or complaints.
- Contact information for someone independent of the research team for problems, concerns, questions, information, or input.
- A statement that participation is voluntary.
- A statement that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.
- If research involves the collection of identifiable information or identifiable biospecimens, an explanation of potential future use. (May be omitted if the research does not involve collection of identifiable information or identifiable biospecimens):
 - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another researcher for future research studies without additional informed consent from the participant or legally authorized representative, if this might be possible; or
 - A statement that the participant's information or specimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
- When the research involves any invasiveness (not including minor invasiveness) and intervention, the fact that the monitor(s), the auditor(s), and the ethical review committee will be granted direct access to the specimens and information acquired from the research subject, without violating confidentiality of the research subjects, to the extent necessary.
- Whether additional disclosures are required for inclusion in the consent process.
 - A statement that the particular treatment or procedure may involve risks to the participant, which are currently unforeseeable.
 - A statement that if the participant is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable.
 - Anticipated circumstances under which the participant's participation may be terminated by the researcher without regard to the participant's consent.
 - Any additional costs to the participant that may result from participation in the research.
 - A statement that significant new findings developed during the course of the research which may relate to the

- participant's willingness to continue participation will be provided to the participant.
- The approximate number of participants involved in the study.
 - A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in this commercial profit.
 - The amount and schedule of all payments.
 - The consequences of a participant's decision to withdraw from the research.
 - Procedures for orderly termination of participation by the participant.
 - A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to the participant, and if so, under what conditions.
 - For research involving biospecimens, a statement specifying whether the research will (if known) or might include whole genome sequencing.

Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.

Written consent must in principle be obtained for research involving invasive procedures, except for the circumstances described below. (Ethical Guidelines, Chapter 5, Part 12)

1. Consent for research to be carried out by acquiring new specimens or information:
 - A. For research involving invasiveness, written consent must be obtained.
 - B. For research not involving invasiveness:
 - a. Research involving intervention: The researcher shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the researcher shall obtain oral informed consent including all required disclosures, and maintain records of methods for providing and content of such information as well as details of consent obtained.
 - b. Research not involving intervention:
 - i. Research utilizing human biological specimens: The researcher shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the researcher shall obtain oral informed consent, including all required disclosures, and maintain records of methods for providing and content of such information as well as details of consent obtained.
 - ii. Research not utilizing human biological specimens: The researcher shall not necessarily be required to obtain informed consent, but when any informed consent is not obtained, the investigator, etc. shall notify the research

subjects, etc. of, or make public, information concerning the research, including the purpose of utilization of information utilized in the research, and opportunities to refuse that the research is commenced or continued on the research subject shall be ensured for the research subjects, etc.

2. Research involving existing specimens or information retained by the research implementing entity:

A. Research utilizing human biological specimens: The investigator, etc. shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the researcher shall obtain oral informed consent, including all required disclosures, and maintain records of methods for providing and content of such information as well as details of consent obtained. If it is difficult to follow these procedures and the case corresponds to any of the following, however, the investigator, etc. may utilize existing specimens or information retained by his/her research implementing entity without these procedures.

a. Cases in which human biological specimens to be utilized in the research have been anonymized (limited to cases in which anonymization has been made, whether linkable or unlinkable and the research implementing entity does not have any decoding index).

b. Cases in which human biological specimens to be utilized in the research do not correspond to the case above (are not anonymized), and if any consent has been obtained for other research, that no indication for utilization in the relevant research is clearly made when the said consent was obtained, each of the following are required:

i. That information including the purpose of utilization of the human biological specimen has been notified to the research subjects, etc. or made public, with respect to implementing the research; and

ii. That above-mentioned other research for which consent has been obtained is reasonably considered as having a significant relation with the purpose of the research;

c. Cases in which human biological specimens to be utilized in the research do not correspond to either case above, all of the following are required:

i. That information including the purpose of utilization of the human biological specimen has been notified to the research subjects, etc. or made public, with respect to implementing the research;

ii. That opportunities to refuse that the research is implemented shall be ensured for the research subjects, etc.; and

iii. That the research is particularly necessary for improvement of public health, and it is difficult to obtain consent of the research subjects, etc.

B. Research not utilizing human biological specimens: The investigator, etc. shall not necessarily be required to obtain informed

consent. When any informed consent is not obtained, however, excepting cases in which information utilized in the research has been anonymized (limited to cases in which anonymization has been made, whether linkable or unlinkable and the research implementing entity does not have any decoding index), the investigators, etc. shall notify to the research subjects, etc. of, or make public, information concerning the research, including the purpose of utilization of information utilized in the research, and opportunities to refuse that the research is implemented shall be ensured for the research subjects, etc.

3. Informed consent when existing specimens or information are to be provided to other research implementing entity(s): The individual providing existing specimens or information to other research implementing entity shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the individual providing existing specimens or information shall obtain oral informed consent, including all required disclosures (including the fact that existing specimens or information are to be provided) and maintain records of methods for providing and content of such information as well as details of consent obtained. If it is difficult to follow these procedures and the case corresponds to any of the following, however, the individual may provide existing specimens or information without these procedures.

When existing specimens or information are provided (not including the cases as defined in the cases), the director of the institution to which the individual providing existing specimens or information belongs (hereinafter referred to as "institution providing existing specimens or information") shall be aware of the content of such specimens or information to be provided.

A. Cases in which existing specimens or information to be provided have been anonymized (limited to cases in which anonymization has been made, whether linkable or unlinkable and the institution does not provide any decoding index).

B. Cases in which the existing specimens or information to be provided do not correspond to A above and the director of the institution providing existing specimens or information has given approval after relevant ethical review committee deliberation, with respect to the compliance status with each of the following requirements;

a. That the following information has been disclosed to the research subjects, etc. or made public, with respect to implementing the research or providing existing specimens or information.

i. The fact that the provision to an individual outside the institution providing specimens or information is the purpose of utilization;

ii. The items of personal information, etc. to be provided to an individual outside of the institution providing existing specimens or information;

- iii. The means or method of provision to an individual outside of the institution providing existing specimens or information; and
 - iv. The fact that the provision of such personal information, etc., as will lead to the identification of the research subjects, to individuals outside of the institution providing existing specimens or information will be discontinued at the request of the research subject or his/her representative.
- b. That opportunities to refuse that the research is implemented have been ensured for the research subjects, etc.

C. When information utilized in research is to be provided for the research of socially high significance and on condition that the provisions in the cases above cannot be complied with for the reason of the method and content of the research, the content of information utilized in research and others, it is required that the director of the institution providing existing specimens or information has approved after relevant ethical review committee deliberation, with respect that other appropriate measures will be taken to the extent necessary. In this case, all requirements as defined below in section 6 are met.

4. Informed consent for research to which existing specimens or information are to be provided in accordance with the procedures as defined in (3) above:

The investigator, etc. shall not necessarily be required to obtain informed consent. When any informed consent is obtained, however, the investigator, etc. shall confirm, with respect to utilization in the research of such specimen or information, that the individual providing existing specimens or information has followed the procedures as defined in (3) above, and the details of such consent obtained from the research subject, etc. (excepting cases in which the specimens or information are provided pursuant to the provisions of laws or ordinances).

In addition, when existing specimens or information which have not been anonymized are utilized (excepting cases in which the investigator, etc. obtains informed consent for the utilization), the investigator, etc. shall make public information concerning the implementation of the research, including handling of such existing specimens or information, and with regards that the research is implemented, opportunities to withdraw such consent shall be ensured for the research subject, etc.

5. Procedures in the research in emergency situations involving obvious life-threatening risk to the research subject. (See Element II.4.C.)

6. Consent may be omitted where all the following conditions are met:

- i. The research to be implemented does not involve invasiveness (not including minor invasiveness);
- ii. The omission of procedures pursuant to the provisions in Section 1 and 2 above is not against research subjects' interests;

- iii. If procedures pursuant to the provisions in Section 1 and 2 above are not omitted, it will be difficult to implement the research or the value of the said research will be significantly undermined; and
- iv. The research to be implemented is recognized as being of socially high significance.

Written materials include a requirement, when consent is not obtained, for the researcher:

- i. To make announcement for the population to which the research subjects, etc. belong, with respect to the purpose of collection and utilization of the specimens or information as well as details (including the method) of such collection and utilization;
- ii. To offer an ex-post explanation to the research subject, etc. promptly (including such explanation made to the group to which the subjects, etc. belong); and
- iii. In the case that the specimens or information are collected or utilized continuously for a long period, the investigator, etc. shall endeavor to make public announcement, with respect to such situation of collection or utilization, including the purposes and methods of collection or utilization of the said specimens or information, in order to make it widely known to society.

Standard II-4: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.

Element II.4.B. The IRB or EC has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.

Written materials describe the process to obtain consent from legally authorized representatives. (Ethical Guidelines, Chapter 4, Part 13)

The research protocol defines:

- i. Criteria for selection of legally acceptable representatives, etc.;
- ii. Information to be provided to the legally acceptable representative, etc.; and
- iii. When the research subject is a child or adult unable to provide consent, the reason why such an individual shall be the research subject.

When the research subject has completed junior high school or other relevant schooling, or is 16 years or older, and is considered to have enough judgment concerning the research to be implemented on him/herself, the investigator, etc. or the individual providing existing specimens or information shall obtain informed consent also from the said research subject in addition to the legally authorized representative.

Element II.4.C. The IRB or EC has and follows written policies and procedures for making exceptions to consent requirements for planned

emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance.

When it is considered necessary to implement research urgently in order to prevent public health-related harm from occurring or spreading, the said chief executive shall submit the matter to the ethical review committee for deliberation without delay after giving approval, and if the ethical review committee forms an opinion that the research shall be suspended or terminated or that revision shall be made in the research protocol, the said chief executive shall respect such opinions and take appropriate measures, such as ordering the principal investigator to suspend or terminate the research or getting the research protocol revised. (Ethical Guidelines, Chapter 3, Part 2)

Emergency research may involve a waiver of consent:

1. Procedures in the research in emergency situations involving obvious life-threatening risk to the research subject:
 - i. The research subject is facing an emergency involving obvious life-threatening risk;
 - ii. When the research involves intervention, currently available treatments are unlikely to achieve sufficient therapeutic effects in the research subject, and there is sufficient possibility of saving the life of the research subject in a life-threatening condition by implementing the said research;
 - iii. The burdens and risks to be caused on the research subjects are minimized; and
 - iv. The legally acceptable representative or the prospective legally acceptable representative cannot immediately be contacted for consent.

Standard II-5: The IRB or EC maintains documentation of its activities.

Element II.5.A. The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures.

Written materials require that EC records for a protocol or research plan include:

- When any significant finding concerning the research subject's health or genetic characteristics which may be inherited by his/her offspring, etc. may be obtained through implementing the research or handling of the research results related to the research subject (including incidental findings) (Ethical Guidelines, Chapter 3, Part 8(1)).
- When the research involves the collection or provision of specimens, EC records must include, in principle, the items below. Any of those items may be omitted, however, when the chief executive of research implementing entity gives approval for that after relevant ethical review committee deliberation.

- Organizational framework for the collection and provision of specimens or information (including name(s) of the organization collecting and providing specimens or information and the investigator(s), etc.);
- Objectives and significance of the collection and provision of specimens or information;
- Method and time period for the collection and provision of specimens or information;
- Types of specimens or information to be collected and provided;
- Procedures pursuant to the provisions in Part 12 below for obtaining informed consent, etc. (including information to be provided and consented to pursuant to the relevant provisions in Part 12, when obtaining informed consent);
- Handling of personal information, etc. (including process of anonymization, when anonymization is conducted);
- Burdens to be caused on the research subjects and predictable risks and benefits, including comprehensive assessment of such burdens, risks, and benefits as well as measures to minimize those burdens and risks;
- Means for storage of specimens or information and for quality control of them;
- Handling of specimens or information after the end of collection and provision;
- Status of research-related conflicts of interest of the organization collecting and providing specimens or information, such as fund resources for the collection and provision, as well as research-related conflicts of interest of each investigator, etc., such as his/her individual income;
- Response to consultation, etc. made by the research subjects, etc. and other individuals concerned;
- When the research involves any medical technique beyond usual medical practice, a statement to that effect and details of such;
- When any significant finding concerning the research subject's health or genetic characteristics which may be inherited by his/her offspring, etc. may be obtained through implementing the research or handling of the research results related to the research subject (including incidental findings); and
- With respect to specimens or information acquired from the research subject, when any of those may be utilized or provided to other research implementing entity(s) for the research in the future that is not identified at the time of obtaining consent from the research subject, etc., a statement to that effect and the contents of utilization assumed at the time of obtaining consent.

(Ethical guidelines, Chapter 3, part 8)

Written materials require that EC records be retained for five years after the date the research has ended or three years after the date the

final publication of the research results are reported, whichever is later. (Ethical Guidelines, Chapter 4, part 10 and Chapter 8, Part 19)

Domain III: Researcher and Research Staff

Standard III-1: In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.

Element III.1.C. Researchers employ sound study design in accordance with the standards of their discipline. Researchers design studies in a manner that minimizes risks to participants.

When a principal investigator has carried out the research which involves any medical technique beyond usual medical practice, the principal investigator, even after the end of the research, shall endeavor to ensure that the research subjects can access the best possible preventive measures, diagnosis and treatment identified by the outcome of the research. (Ethical Guidelines, Chapter 2, Part 5)

Standard III-2: Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the organization's policies and procedures for protecting research participants; and the IRB's or EC's determinations.

Element III.2.D. Researchers and Research Staff follow reporting requirements in accordance with applicable laws, regulations, codes, and guidance; the organization's policies and procedures; and the IRB's or EC's requirements.

When conducting interventional research, researchers must register research with a public database operated by National University Hospital Council of Japan, the Japan Pharmaceutical Information Center, or the Japan Medical Association. The chief executive may grant approval to not include certain information if confidentiality is necessary to protect the human rights of research participants. (Ethical Guidelines, Chapter 3, Part 9)

When the principal investigator has finished research, the principal investigator shall, without delay, make public the results of the research, having taken necessary measures to protect human rights of the research subject, etc. and other individuals concerned and rights and interests of the investigator, etc. and other entities concerned. In addition, if the research involves invasiveness (not including minor invasiveness) and intervention, the principal investigator shall, without delay, report to the chief executive of the research implementing entity,

when the final publication of results of the research has been made.
(Ethical Guidelines, Chapter 3, Part 9)

Reserachers must report to the chief executive in addition to the
Ethical Review Committee:

- When a researcher becomes aware of any serious concern with respect to human rights of the research subject, or with respect to implementing of the research, such as leakage of information related to the research, the investigator, etc. shall report promptly to the chief executive of research implementing entity and the principal investigator. (Ethical Guidelines, Chapter 2, Part 4, (1)(5))
- When a researcher becomes aware of any fact or obtains any information that appropriateness of implementing the research he/she is engaged in or the reliability of results of the research is, or might be, impaired. (Ethical Guidelines, Chapter 2, Part 4, (2)(3))
- When a principal investigator becomes aware of any fact or obtains any information that ethical justification or scientific validity of the research is, or might be, impaired, and if the continuation of the research will be hindered. (Ethical Guidelines, Chapter 2, Part 5, (2)(3))
- When any adverse event occurs in the implementation of the research, in accordance with specifications prescribed in the research protocol, and the progress of research. (Ethical Guidelines, Chapter 2, Part 5, (2)(6))
- When the research is finished. (Ethical Guidelines, Chapter 2, Part 5, (2)(7))