

Provisional Translation (as of March 2015)

Ethical Guidelines for Medical and Health Research Involving Human Subjects

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Preamble

Medical and health research involving human subjects contributes significantly to society in terms of maintaining and promoting people's good health and advancing patients' recuperation from injury and disease as well as quality of life, through the development of medical and health science and medical technology. Furthermore, such research also acts an important foundation which leads to progress in good health and welfare for society. In this sense, on the one hand, it is required that an institutional framework be developed and maintained in which investigators can carry out research appropriately and smoothly under academic freedom. On the other hand, medical and health research involving human subjects can have a major impact on such research subjects both physically and mentally or, indeed, on society itself, as well as cause a variety of ethical, legal and social problems. The welfare of those research subjects shall be given priority over scientific and social results of research, and human dignity and rights shall be protected.

From this point of view, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare established the Ethical Guidelines for Epidemiological Research (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare No. 1 of 2007), originally in 2002 and later amended entirely in 2007, and the

Ethical Guidelines for Clinical Research (Public Notice of the Ministry of Health, Labour and Welfare No. 415 of 2008), originally in 2003 and later amended entirely in 2008, in order that investigators can respect and protect human dignity and rights as well as carry out research appropriately and smoothly. Both guidelines were based on the Constitution of Japan, the Act on the Protection of Personal Information and other related acts, and the ethical principles as defined in the Declaration of Helsinki adopted by the World Medical Association, etc. In recent years, however, research falling under the above-mentioned guidelines has become more and more diversified and the objectives and methods of such research are increasingly becoming common in both of the above-mentioned guidelines and hence, it has been pointed out that the scope of those guidelines are not clear enough. Now, therefore, it has been decided to establish new ethical guidelines to merge the previously in place guidelines above.

The new Guidelines provide fundamental requirements to be observed by any of those concerned in medical and health research involving human subjects. The chief executive of a research implementing entity is required to make decision on the appropriateness of the research protocol prepared by principal investigator, prior to the implementation of the research, having deliberation by relevant ethical review committee, while investigators, etc. are required to implement their research appropriately in accordance with the research protocol approved by chief executive of research implementing entity. These new Guidelines only set basic rules, taking into consideration that medical and health research involving human subjects can take a variety of forms. It is required that all individuals concerned, such as investigators, etc., the chief executive of a research implementing entity and members of ethical review committee shall have high-level ethical standards and carry out each responsibility in compliance with these rules in order that their research can contribute to society by obtaining understanding and trust from society.

Chapter 1 General Provisions

Part 1 Purpose and Basic Principles

The purpose of these Guidelines is to ensure that human dignity and rights be protected and that medical and health research involving human subjects be promoted appropriately, by prescribing the rules and procedures with which those who are concerned in such research should comply. Any of those concerned in this type of research shall carry out their research, in accordance with these Guidelines as basic principles for the matters as defined below:

- (i) Implementation of research with social and academic values;

- (ii) Ensuring of scientific validity suitable to the characteristics in the particular field of research;
- (iii) Comprehensive assessment of the burdens on research subjects and predicted risks and benefits;
- (iv) Review by an independent and fair ethical review committee;
- (v) Adequate prior explanation and voluntary informed consent of research subjects;
- (vi) Special consideration for vulnerable subjects;
- (vii) Protection of personal information, etc.; and
- (viii) Ensuring of integrity and transparency of research.

Part 2 Glossary

The terms used in these Guidelines shall be defined as follows:

(1) Medical and Health Research Involving Human Subjects

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. In these Guidelines, the term "research" refers to the above-defined medical and health research involving human subjects, when it is mentioned without any specific remark.

(2) Invasiveness

To cause injuries or distress to research subjects' body and/or mind by conducting a procedure for investigational purpose, such as puncture, incision, administration of drugs, irradiation and questions related to the subject's mental trauma, etc.

Of various types of invasiveness, one causing minor injury and/or distress on the research subjects' body and/or mind is called "minor invasiveness."

(3) Intervention

A practice for investigational purpose to control the presence or absence of factors, which can affect a variety of events occurring in relation with human health (including activities to maintain and promote good health and medical practices such as medication and examinations for prevention, diagnosis and treatment of the patients), or the degree of such factors. The above-defined intervention also includes medical technique beyond usual medical practice that is conducted for investigational purpose.

(4) Human Biological Specimen

A part of human body (including that of deceased individuals) to be utilized (or which has been utilized) in research, such as blood, body fluids, tissues, cells, excrement and DNA extracted from these, etc.

(5) Information Utilized in Research

Information on human health, such as the name of disease, details of medication and results of examination and measurement obtained through diagnosis and treatment of research subjects, and other information (including that concerning deceased individuals) to be utilized (or which have been utilized) in research.

(6) Specimen and/or Information

The above-defined human biological specimen and/or the above-defined information utilized in research.

(7) Existing Specimen and/or Information

Of the above-defined specimen and/or information, specimen and/or information which corresponds to any of the following:

- (i) Specimen and/or information already existing prior to the preparation of the research protocol; or
- (ii) Specimen and/or information acquired after the preparation of the research protocol however not intended to be utilized in the research defined in the research protocol at the time the said specimen and/or information were acquired.

(8) Research Subject

A person (including deceased individual) who corresponds any of the following descriptions:

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

(9) Research Implementing Entity

A legal entity, administrative organ or individual business owner who carries out research, not including contractors for a part of research work such as storage of specimens and/or information and statistical processing.

(10) Collaborative Research Implementing Entity

A research implementing entity collaboratively conducting research in accordance with the research protocol, including any entities which newly acquire specimens or information from research subjects for the said research and provide the above to other research implementing entity(s).

(11) Organization Collecting and Providing Specimens or Information

Of the above-defined research implementing entities, an organization which conducts research work to acquire specimens or information from research subjects or from other entity(s), to retain and to provide the said specimens or information to other research implementing entity(s) repeatedly and on an ongoing basis.

(12) Investigator, etc.

Principal investigator(s) and others who are engaged in implementing of research (including the execution of operations at the above-defined “organization collecting and providing specimens or information”), not including individuals who do not belong to research implementing entities and are engaged only in the provision of existing specimens or information or in part in entrusted research work.

(13) Principal Investigator

An individual who is engaged in implementing of research and directing overall research work at the research implementing entity he/she belongs to.

(14) Chief Executive of Research Implementing Entity

The representative of a legal entity, the head of an administrative organ or an individual business owner who carries out research.

(15) Ethical Review Committee

An organization utilizing a consensual decision making system, which is organized to make examination and reviews concerning the ethical justification and scientific validity to commence or continue research and other relevant matters.

(16) Informed Consent

Consent to be given voluntarily by research subjects or their legally acceptable representative, etc. to investigators, etc. or individuals providing existing specimens or information, with respect to whether the research shall be commenced or continued (including how specimens or information shall be handled), having enough understanding after receiving adequate prior information with regard to the purpose and significance of the research, burdens on the research subjects and predicted results of the research (including both risks and benefits), etc.

(17) Legally Acceptable Representative

An individual expected to speak for the will and benefit of a living research subject, and if the research subject is considered objectively unable to give informed consent, competent to give informed consent to investigators, etc. or individuals providing existing specimens or information on behalf of the said research subject.

(18) Legally Acceptable Representative, etc.

An individual including the above-defined legally acceptable representative as well as individual who is competent to give informed consent on behalf of the deceased research subject.

(19) Informed Assent

Expression of agreement, with respect to whether the research shall be commenced or continued, of research subjects who are considered

objectively unable to give informed consent after having been given information concerning the research to be commenced or continued in an intelligible language depending on the subjects' level of comprehension.

(20) Personal Information

Information about a living individual which can identify the specific individual by name, date of birth, or other description contained in such information, including such information as will allow easy reference to other information and will thereby enable the identification of the specific individual.

(21) Personal Information, etc.

Information including the above-defined personal information as well as information about a deceased individual, which can identify the specific deceased individual.

(22) Anonymization

Removal from the above-defined personal information, etc. of all or part of descriptions, etc. which enable identification of a specific individual (including a specific deceased individual; the same applies hereinafter) and assignment of symbols or numbers irrelevant to the said specific individual in place of such removed descriptions.

The above-defined anonymization also includes the process of removing all or part of information, even if such information by itself does not enable identification of any specific individuals, which will enable identification of a specific individual if referred to other information available in order to ensure that the said information cannot enable such identification.

(23) Linkable Anonymization

Anonymization to enable identification of each specific individual when required, by retaining a decoding index which is a list of the specific individuals' identification and the corresponding symbols or numbers given to each individual.

(24) Unlinkable Anonymization

Anonymization to disable identification of each specific individual, by

not retaining a decoding index listing the specific individuals' identification and the corresponding symbols or numbers given to each individual.

(25) Adverse Event

Any unfavorable and unintended injury and illness or any sign of such (including an abnormal laboratory finding) caused to research subjects, regardless of whether there is or is not any causal relation with the research implemented.

(26) Serious Adverse Event

Of the above-defined adverse events, an event that:

- (i) Results in death;
- (ii) Is life-threatening;
- (iii) Requires inpatient hospitalization or prolongation of existing hospitalization;
- (iv) Results in persistent or significant disability or incapacity; or
- (v) Is a congenital anomaly or birth defect to offspring.

(27) Unexpected Serious Adverse Event

Of the above-defined serious adverse events, an event 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.

(28) Monitoring

An act of overseeing the progress of research, and of determining whether the research is being conducted in compliance with these Guidelines and the research protocol, in order to ensure that the research is properly conducted. Such act is performed by an individual appointed by the principal investigator.

(29) Audit

An examination of research-related activities to determine whether the research has been conducted in compliance with these Guidelines and the research protocol, in order to assure the reliability of results of the research. Such examination is performed by an individual appointed by the principal

investigator.

Part 3 Scope of Application

1. Research applicable to these Guidelines

These Guidelines shall apply to any medical and health research involving human subjects which is carried out by a Japanese research implementing entity or carried out in Japan. Of research which falls under the scope to which other guidelines are applicable, however, matters not set forth in such other guidelines shall be carried out in accordance with these Guidelines.

Besides, these Guidelines shall not apply to research which corresponds to any of the following:

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

2. Research carried out outside Japan

- (1) When carrying out research outside Japan (including when conducting research collaboratively with foreign research implementing entities), a Japanese research implementing entity shall follow these Guidelines and also adhere to the provisions set forth in local laws, ordinances, guidelines, etc. When the provision(s) set forth in such local laws, ordinances, guidelines, etc. are stricter than the provision(s) of these Guidelines, however, research shall be carried out in accordance with the provision(s) of the said local laws, ordinances, guidelines, etc. in place of the relevant provision(s) of these Guidelines.
- (2) When the provision(s) of these Guidelines are stricter than the provision(s) of local laws, ordinances, guidelines, etc. and it is difficult to carry out research in accordance with the provision(s) of these Guidelines, if the following is prescribed in the research protocol and the chief executive of Japanese research implementing entity gives approval after relevant ethical

review committee deliberation with respect to the implementation of the research, the said research may be carried out in accordance with the provision(s) of local laws, ordinances, guidelines, etc. in place of the relevant provision(s) of these Guidelines.

- (i) Appropriate measures to be taken with respect to informed consent at the overseas research implementing sites; and
- (ii) Appropriate measures to be taken to protect and safeguard personal information, etc. acquired in relation with implementation of the research at the overseas research implementing sites.

Chapter 2 Obligations of Investigators, etc.

Part 4 Basic Obligations of Investigators, etc.

1. Consideration for research subjects, etc.

- (1) Investigators, etc. shall carry out research with the utmost respect for the life, health and human rights of research subjects.
- (2) In principle, investigators, etc. shall obtain informed consent prior to implementing research.
- (3) Investigators, etc. shall respond appropriately and promptly to consultation, inquiries, complaints, etc. (hereinafter referred to as “consultation, etc.”) of research subjects or their legally acceptable representatives, etc. (hereinafter referred to as “research subjects, etc.”) and other individuals concerned.
- (4) Investigators, etc. shall not disclose information obtained while they are engaged in research without justifiable reason. The same shall apply even after investigators, etc. are no longer engaged in the research.
- (5) When an investigator, etc. becomes aware of any serious concern with respect to human rights of the research subject, etc. 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.

2. Ensuring, etc. of ethical justification and scientific validity of research

- (1) Investigators, etc. shall carry out research appropriately, complying with laws, ordinances, guidelines, etc. and in accordance with the research protocol reviewed by the ethical review committee and approved by the chief executive of the research implementing entity.

- (2) When an investigator, etc. becomes aware of any fact or obtains any information that ethical justification or scientific validity of the research he/she is engaged in is, or might be, impaired (not including cases which correspond to (3) below), the investigator, etc. shall report promptly to the principal investigator.
- (3) When an investigator, etc. 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, the investigator, etc. shall promptly report to the principal investigator or the chief executive of the research implementing entity.

3. Education and training

Investigators, etc. shall receive education and training on the ethics of research and on knowledge and skills necessary to carry out the research prior to its implementation. They shall also receive education and training during the research period on a regular basis as necessary.

Part 5 Obligations of Principal Investigator

1. Preparation of research protocol and compliance of investigators, etc.
 - (1) The principal investigator shall prepare an appropriate research protocol prior to any implementation of research. In the same manner, the principal investigator shall revise the research protocol prior to any implementation of a changed conduct of research.
 - (2) The principal investigator shall prepare a research protocol to ensure ethical justification and scientific validity of the research. In addition, when preparing the research protocol, the principal investigator shall comprehensively assess the burdens on research subjects and predicted risks and benefits as well as take measures to minimize such burdens and risks.
 - (3) When the principal investigator intends to carry out research which involves invasiveness (not including minor invasiveness) along with medical technique beyond usual medical practice, the principal investigator shall take beforehand necessary measures, such as purchasing insurance, etc., in preparation for compensation to the research subject in the event of research-related injuries, appropriately.
 - (4) Pursuant to the provisions in Part 9 of these Guidelines below, the

principal investigator shall appropriately register the summary of his/her research and other related information, and make results of the research public.

- (5) The principal investigator shall instruct and manage other investigators and those concerned in his/her research implementing entity, in order that the research shall be appropriately carried out in compliance with the research protocol and that reliability of results of the research can be secured.
2. Management and supervision of research progress and identification and reporting adverse events, etc.
- (1) The principal investigator shall endeavor to take action in order that his/her research shall be carried out appropriately and the reliability of results of the research can be secured, for example, by collecting information necessary in carrying out the research.
 - (2) 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 (not including cases which correspond to (3) below), the principal investigator shall report to the chief executive of the research implementing entity without delay and, as necessary, suspend or terminate the research or revise the research protocol.
 - (3) When a principal investigator becomes aware of any fact or obtains any information that appropriateness of implementing the research he/she is engaged in or reliability of results of the research is, or might be, impaired, the principal investigator shall report to the chief executive of the research implementing entity promptly and, as necessary, suspend or terminate the research or revise the research protocol.
 - (4) In the course of implementing research, when it is considered that predicted risks are larger than expected benefits of the research or it is considered that a satisfactory outcome has been achieved or that such an outcome cannot be achieved, the principal investigator shall terminate the said research.
 - (5) When a principal investigator becomes aware of any serious adverse event which occurs in implementing of research and involves any invasiveness, the principal investigator shall promptly take relevant measures.

- (6) The principal investigator shall report to the chief executive of the research implementing entity, with respect to the progress of the research and status of any adverse event which occurs in implementing of the research, in accordance with specifications prescribed in the research protocol.
- (7) When research is finished (including the case of discontinuance; the same applies hereinafter), the principal investigator of the research shall report to the chief executive of the research implementing entity with respect to matters required.
- (8) When conducting research collaboratively with other research implementing entity(s), the principal investigator shall share relevant information to the research with the principal investigator of such other research implementing entity(s).

3. Following-up research subjects after end of research

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.

Part 6 Obligations of the Chief Executive of Research Implementing Entity

1. Overall supervision of research

- (1) 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.
- (2) 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.
- (3) 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.
- (4) 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).

2. Arrangement, etc. of systems and procedures for implementation of research
 - (1) The chief executive of research implementing entity shall arrange systems and procedures necessary for the appropriate implementation of research.
 - (2) 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.
 - (3) The chief executive of research implementing entity shall ensure that information concerning its research, including results of the research, shall be made public appropriately.
 - (4) 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.
 - (5) 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.
 - (6) 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.

3. Approval, etc. of research
 - (1) When the chief executive of research implementing entity is asked by 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 ethical review committee for deliberation and make decision on relevant measures, such as approval, disapproval, etc., to the matter with due respect to opinions presented by the ethical review

committee.

- (2) When the chief executive of research implementing entity has received any report from principal investigator or other investigators, etc. concerning facts or information deemed to affect the propriety of continuance of a 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.
 - (3) The chief executive of research implementing entity shall provide cooperation with the investigation carried out by relevant ethical review committee.
 - (4) 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.
 - (5) When the chief executive of research implementing entity has received any report from 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.
4. Report, etc. to the Minister(s)
- (1) 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.
 - (2) 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) (hereinafter referred to as the “Minister(s), etc.”) to confirm that the research carried out by the research implementing entity is complying with these Guidelines.

- (3) 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.

Chapter 3 Research Protocol

Part 7 Procedures Related to Research Protocol

1. Preparation and revision of research protocols
 - (1) When principal investigator intends to carry out any research (including the case in which research is implemented after revision(s) in the research protocol; the same applies hereinafter), the principal investigator shall prepare the research protocol beforehand and receive approval of the chief executive of the research implementing entity.
 - (2) When principal investigator intends to conduct any research collaboratively with other research implementing entity(s), the principal investigator shall clarify the role and responsibility of the principal investigators of each of other collaborative research implementing entity(s), in the course of the preparation of a research protocol.
 - (3) When principal investigator intends to entrust a part of work related to research to be carried out by the research implementing entity he/she belongs to, the principal investigator shall prescribe which work shall be entrusted in the course of preparation of the research protocol.
2. Submission of matters to ethical review committee for deliberation
 - (1) When principal investigator asks for approval for any implementation of research at the research implementing entity, the chief executive of the research implementing entity shall submit the matter to ethical review committee for deliberation with respect to appropriateness of implementing the research. The said chief executive may decide to give

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.

- (2) When the chief executive of research implementing entity submits a matter to ethical review committee for deliberation concerning research to be conducted collaboratively with other research implementing entity(s), the said chief executive shall provide the committee with information necessary for making reviews, including information on approval for the implementation of research at other collaborative research implementing entity(s), results of the review by other ethical review committee(s) and the progress status of the research.
- (3) 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).

3. Approval by chief executive of research implementing entity

The chief executive of research implementing entity shall respect opinions of ethical review committee and make decision on whether the implementation of the research should be approved or not and on other measures necessary in relation with the research. In the course of such decision, 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.

4. Procedures after end of research

- (1) When principal investigator has finished any research, the principal investigator shall submit to the chief executive of the research implementing entity without delay, in writing, a statement to that effect

and a summary of the results of the research.

- (2) When the chief executive of research implementing entity has received a report from principal investigator pursuant to the provisions of (1) above, the said chief executive shall report, in writing, a statement to the effect that the research has been finished and summarized results of the research, to the ethical review committee which made reviews on the research.

Part 8 Contents of Research Protocol

- (1) Contents of research protocol (not including cases as defined in (2) below) shall, in principle, include the items below. Any of those items may be omitted, however, when the chief executive of the research implementing entity gives approval for that after relevant ethical review committee deliberation.
 - (i) Title of the research;
 - (ii) Site-specific information for the research (including names of the research implementing entity(s) and the investigator(s), etc.);
 - (iii) Objectives and significance of the research;
 - (iv) Method and time period of the research;
 - (v) Enrolling Criteria of research subjects;
 - (vi) Basis of scientific validity for implementing the research;
 - (vii) 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);
 - (viii) Handling of personal information, etc. (including process of anonymization, when anonymization is conducted);
 - (ix) Burdens to be caused on the research subjects and predicted risks and benefits, including comprehensive assessment of such burdens, risks and benefits as well as measures to minimize those burdens and risks;
 - (x) Means for storage and disposal of specimens and information (including records related to information utilized in research);
 - (xi) Matters to be reported to the chief executive of the research implementing entity and procedures for such reports;
 - (xii) Status of research-related conflicts of interest of the research implementing entity, such as research fund resources, as well as

- research-related conflicts of interest of each investigator, etc., such as his/her individual income;
- (xiii) Means to disclose information on research;
 - (xiv) Means to respond to the consultation, etc. made by the research subjects, etc. and other individuals concerned;
 - (xv) When obtaining informed consent from legally acceptable representative, etc., procedures pursuant to the provisions in Part 13 below (including matters related to the criteria to select legally acceptable representatives, etc. and to be informed and consented to pursuant to the provisions in Parts 12 and 13 below);
 - (xvi) When obtaining informed assent, procedures pursuant to the provisions in Part 13 below (including information to be provided);
 - (xvii) When the research is to be implemented pursuant to the provisions in Part 12.5 below, means to determine on conformity of all requirements set forth in the Section;
 - (xviii) When the research involves any financial expenditure on or remuneration for the research subject, etc., a statement to the effect that and details of such;
 - (xix) When the research involves invasiveness (not including minor invasiveness), means to respond in cases of serious adverse event;
 - (xx) When the research involves any invasiveness, whether or not compensation will be offered for research-related injury and detail of such compensation;
 - (xxi) When the research involves any medical technique beyond usual medical practice, response related to the healthcare delivery to the research subjects after the research;
 - (xxii) 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, handling of the research results related to the research subject (including incidental findings);
 - (xxiii) When a part of work related to the research is entrusted, the content of work to be entrusted and means of supervision over the contractor(s);
 - (xxiv) With respect to specimens and 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 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; and

(xxv) When monitoring or audit is performed pursuant to the provisions in Part 20 below, organizational framework and procedures for such.

(2) Contents of the research protocol for operating research work acquiring specimens or information from research subjects or being provided from other entities, and retaining and providing such specimens or information to other research implementing entities repeatedly and continuously (hereinafter referred to as “collection and provision”) shall, in principle, include 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.

- (i) 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.);
- (ii) Objectives and significance of the collection and provision of specimens or information;
- (iii) Method and time period for the collection and provision of specimens or information;
- (iv) Types of specimens or information to be collected and provided;
- (v) 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);
- (vi) Handling of personal information, etc. (including process of anonymization, when anonymization is conducted);
- (vii) 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;
- (viii) Means for storage of specimens or information and for quality control of them;

- (ix) Handling of specimens or information after the end of collection and provision;
- (x) 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;
- (xi) Response to consultation, etc. made by the research subjects, etc. and other individuals concerned;
- (xii) When the research involves any medical technique beyond usual medical practice, a statement to that effect and details of such;
- (xiii) 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, handling of the research results related to the research subject (including incidental findings); and
- (xiv) 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 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.

Part 9 Registration and Publication of Research

1. Registration of summary of research protocol and results

When the principal investigator intends to carry out any research which involves intervention, the principal investigator shall, prior to the implementation of the research, register a summary of the research in a public database operated by the National University Hospital Council of Japan, the Japan Pharmaceutical Information Center, or the Japan Medical Association, shall update the registered contents appropriately according to revisions of the research protocol or the progress of the research, and shall register, without delay, the results of the research when the research is finished. Any of contents may be omitted from the registration, however, when the chief executive of the research implementing entity gives approval for that, by reason that 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, after relevant ethical review committee deliberation.

2. Publication of research results

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 entity 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 made.

Chapter 4 Ethical Review Committee

Part 10 Organizing, etc. of Ethical Review Committee

1. Qualifications for organizing ethical review committee

The organizer of ethical review committee shall meet the following qualifications:

- (i) Being capable of performing administrative work related to review appropriately;
- (ii) Having the capacity for sustainable operation of the ethical review committee; and
- (iii) Having the competence to operate the ethical review committee in a neutral and fair manner.

2. Obligations of organizer of ethical review committee

- (1) The organizer of ethical review committee shall prescribe the organizational structure of the committee and rules to operate the committee as well as ensure members of the ethical review committee and other individuals engaged in administrative work perform their duties in accordance with the said rules.
- (2) The organizer of ethical review committee shall appropriately retain review materials concerning the research which the ethical review committee has examined until the end of the said research is reported (when the research involves invasiveness (not including minor invasiveness) and intervention, the review materials shall be retained for

five (5) years from the date the end of the said research is reported).

- (3) When beginning operation of ethical review committee, the organizer of the committee shall make public, in the Ethical Review Committee Reporting System, the organization of, provisions for operating and list of members of the committee.

In addition, the said organizer shall similarly make public, in the Ethical Review Committee Reporting System, 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.

- (4) The organizer of ethical review committee shall take necessary measures to ensure that members of the ethical review committee and other individuals engaged in administrative work receive education and training concerning relevant reviews and other related duties.
- (5) The organizer of ethical review committee shall provide cooperation with the inspection carried out by the Minister(s), etc. on the compliance of the ethical review committee's organization and operation with these Guidelines.

Part 11 Roles, Responsibilities, etc. of Ethical Review Committee

1. Roles and responsibilities

- (1) When the chief executive of research implementing entity asks for any opinion with regard to the appropriateness of implementing research or other matters, the ethical review committee shall make reviews on the matter, in accordance with these Guidelines, neutrally and fairly including information on any conflicts of interest of the research implementing entity and the investigator etc. as well as from ethical and scientific viewpoints, and shall present its opinions in writing.
- (2) The ethical review committee may make a necessary investigation from ethical and scientific viewpoints on the research it makes reviews of pursuant to the provisions of (1) above, and may present relevant opinions to the chief executive of the research implementing entity, with respect to revisions of the research protocol, termination of the research and other

matters related to the research.

- (3) Of the research it has made reviews of pursuant to the provisions of (1) above, for the research which involves invasiveness (not including minor invasiveness) and intervention, the ethical review committee may make a necessary investigation to secure the appropriateness of implementing the research and the reliability of results of the research, and may present relevant opinions to the chief executive of the research implementing entity, with respect to revisions of the research protocol, termination of the research and other matters related to the research.
 - (4) Members of ethical review committee and individuals engaged in the administrative work shall not disclose, without justifiable reason, any information obtained during the duties related to the committee. The same shall apply, even after they cease to be engaged in the duties.
 - (5) When a member of ethical review committee or an individual engaged in the administrative work becomes aware of any serious concern with respect to human rights of the research subject, etc. or with respect to the appropriateness for implementing the research which the committee made reviews of pursuant to the provisions of (1) above, such as leakage of information related to such research, as well as with respect to the neutrality or fairness of its reviews, the said member or individual shall report promptly to the organizer of the committee.
 - (6) Members of ethical review committee and individuals engaged in the administrative work shall receive education and training to acquire knowledge necessary for reviews from ethical and scientific viewpoint, etc. prior to being engaged in reviews or other related duties. They shall also receive education and training later than that, on a regular basis as necessary.
2. Composition and quorum, etc.
- (1) The composition of ethical review committee shall meet each of the following requirements in order that the duties of the committee, such as reviews of research protocols, be executed appropriately. Those members as defined in each of the groups of (i) to (iii) below cannot concurrently hold status for other groups. The same requirements shall apply to the quorum of the committee's meetings.
 - (i) The committee shall have a member who is expert in natural science,

such as a medicine and medical care professional, etc.;

- (ii) The committee shall have a member who is expert in humanities and social sciences, such as a professional in ethics and law, etc.;
 - (iii) The committee shall have a member who can provide opinions of the general public, including viewpoints of research subjects;
 - (iv) The committee shall have at least two members who do not belong to the organization to which the organizer of the committee belongs;
 - (v) The committee shall have both male and female members; and
 - (vi) The committee shall have five or more members.
- (2) Investigators, etc. engaged in the research which is subject to deliberation shall not be present when the deliberation and adoption of opinions are made at the committee's meeting. When so requested by the ethical review committee, however, such investigators, etc. may attend the meeting to provide information on the said research.
- (3) 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.
- (4) The ethical review committee may invite nonmembers with expertise in special areas for assistance depending on matters subject to review and content of such.
- (5) When reviewing the research protocol of which research subjects are those who need special considerations and presenting its opinions on such research, the ethical review committee shall, as necessary, seek opinions of experts who have discernment on such research subjects.
- (6) The ethical review committee shall endeavor to make adoption of its opinions unanimously.

3. Expedited review

Under any of the following circumstances the ethical review committee may delegate reviews to member(s) designated by the committee (hereinafter referred to as "expedited review") and adopt their opinion. The result of such an expedited review shall be considered as the conclusion of the entire ethical

review committee and shall be reported to other members of the committee.

- (i) 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;
 - (ii) Review of minor revisions of research protocol;
 - (iii) Review of the research which does not involve any invasiveness and intervention; or
 - (iv) Review of the research which involves minor invasiveness but does not involve any intervention.
4. Review of research to be carried out by other research implementing entity(s)
- (1) When the chief executive of research implementing entity submits the matters for deliberation by the ethical review committee which is organized by the institution he/she belongs to, the said ethical review committee shall have enough information concerning the site-specific information for the research at the research implementing entity, in order to make reviews and present its opinions.
 - (2) With respect to research carried out by other research implementing entity(s) than the institution to which the organizer of the ethical review committee belongs, when the chief executive of the said research implementing entity requests the ethical review committee to continue to make reviews after the committee has made reviews on the same research, the said ethical review committee shall make reviews and present its opinions.

Chapter 5 Informed Consent, etc.

Part 12 Procedures for Obtaining Informed Consent, etc.

1. Procedures, etc. for obtaining informed consent

The investigator, etc. who intends to carry out any research and the individual providing existing specimens or information who intends to provide any of those shall, in principle, obtain informed consent beforehand in accordance with specifications prescribed in the research protocol approved by the chief executive of the research implementing entity and following procedures as defined below, respectively. This, however, shall not apply to

providing of existing specimens or information pursuant to the provisions of laws and ordinances.

(1) Informed consent for research to be carried out by acquiring new specimen or information:

A. Research involving invasiveness:

The investigator, etc. shall obtain informed consent in writing which includes information to be provided pursuant to the provisions in Section 3 below.

B. Research not involving invasiveness:

(a) Research involving intervention:

The investigator, etc. shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the investigator, etc. shall obtain oral informed consent, with respect to the information provided pursuant to the provisions in Section 3 below, 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 investigator, etc. shall not necessarily be required to obtain informed consent in writing. When any written informed consent is not obtained, however, the investigator, etc. shall obtain oral informed consent, with respect to the information provided pursuant to the provisions in Section 3 below, 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 investigator, etc. 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) Informed consent in cases where the research is to be carried out utilizing

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 investigator, etc. shall obtain oral informed consent, with respect to the information provided pursuant to the provisions in Section 3 below, 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 above (a), 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 of (a) and (b) 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 in is not obtained, however, the individual providing existing specimens or information shall obtain oral informed consent, with respect to the information provided pursuant to the provisions in Section 3 below (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 B and C below), 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 notified 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 A and B 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 in Section 6 (1) (i) to (iv) below shall be met. In addition, of measures as defined in Section 6 (2) (i) to (iii) below, appropriate measures shall be taken.

- (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.

2. Revising research protocol

When the investigator, etc. is carrying out the research of which protocol has been revised, the investigator, etc. shall, anew in principle, follow procedures concerning informed consent pursuant to the provisions in Section 1 above. Any informing of such revision and subsequent consent may be omitted, however, when the chief executive of the research implementing entity gives approval for that after by relevant ethical review committee deliberation.

3. Information to be provided to research subjects, etc.

When obtaining informed consent from a research subject, etc., Information to be provided to the research subject, etc. shall, in principle, include the items below. Any of those items may be omitted, however, when the chief executive of the research implementing entity gives approval for that after relevant ethical review committee deliberation.

- (i) Title of the research and the fact that approval of the chief executive of the research implementing entity has been given concerning its implementation;
- (ii) 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));
- (iii) Objectives and significance of the research;
- (iv) Method and time period of the research (including purpose of the utilization of specimens or information acquired from the research subject);
- (v) Reasons why asked to be enrolled in the research;
- (vi) Burdens to be caused on the research subjects and predictable risks and benefits;
- (vii) The fact that research subjects, etc. may withdraw their consent at any time even after they have given consent with regard that the research is commenced or continued (when it can be difficult to take measures that follow the withdrawal made by the research subject, etc., a statement to that effect and the reason for the difficulty);
- (viii) The fact that the refusal or withdrawal of consent by a research subject, etc. with regard that the research is to be commenced or continued does not cause any disadvantage to such research subject, etc.;
- (ix) Means to make information on the research public;
- (x) 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 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;
- (xi) Handling of personal information, etc. (including process of anonymization, when anonymization is conducted);

- (xii) Means for storage and disposal of specimens and information;
 - (xiii) Status of research-related conflicts of interest of the research implementing entity, such as research fund resources, as well as research-related conflicts of interest of each investigator, etc., such as his/her individual income;
 - (xiv) Response to consultation, etc. made by research subjects, etc. and other individuals concerned;
 - (xv) When the research involves any financial expenditure on or remuneration for the research subject, etc., a statement to that effect and details of such;
 - (xvi) When the research involves any medical technique beyond usual medical practice, description of alternative procedure(s) or course(s) of treatment;
 - (xvii) When the research involves any medical technique beyond usual medical practice, response related to the healthcare delivery to the research subjects after the research;
 - (xviii) 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, handling of the research results related to the research subject (including incidental findings);
 - (xix) When the research involves any invasiveness, whether or not compensation will be offered for research-related injury and details of such compensation;
 - (xx) With respect to specimens and 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 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; or
 - (xxi) 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.
4. Procedures to utilize specimens and information in research unidentified at the time consent was given
- When the investigator, etc. has provided the information including purpose of

the utilization of specimens and information which is presumed at the time of obtaining consent of the research subject, etc. as fully as possible, and when, later, such purposes of the utilization, etc. are newly identified, the investigator, etc. shall notify the research subjects, etc. of, or make public, information including the newly identified purposes of the utilization, etc. in accordance with the specifications prescribed in the prepared or revised research protocol, 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

When the investigator, etc. considers that the research subject fulfills all the following conditions, in accordance with specifications prescribed in the research protocol, the investigator, etc. may enroll such research subject without obtaining consent of the research subjects, etc. When such research is implemented, however, the investigator, etc. shall promptly follow procedures to obtain written informed consent including the information to be provided pursuant to the provisions in Section 3 above.

- (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.

6. Omission of procedures concerning informed consent, etc.

- (1) When carrying out the research which corresponds to all of the requirements as defined below, the investigator, etc. or the individual providing existing specimens or information may omit all or part of the procedures pursuant to the provisions in Section 1 and 2 above, in accordance with specifications prescribed in the research protocol approved by the chief executive of the research implementing entity.

- (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.
- (2) When any procedure(s) pursuant to the provisions in Section 1 and 2 above is to be omitted pursuant to the provisions of (1) above, the investigator, etc. shall take appropriate measures among those defined below.
- (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.

7. Withdrawal of consent, etc.

When a research subject, etc. offers a withdrawal or refusal of consent corresponding to any of the following, the investigator, etc. shall, without delay, take appropriate measures in accordance with the withdrawal or refusal as well as provide explanation on such measures to the research subjects, etc. The investigator, etc., is not necessarily required to take such measures, however, when it is difficult and the chief executive of the research implementing entity approves that such measures should not be taken after relevant ethical review committee deliberation. In this case, the investigator, etc. shall endeavor to provide explanation to the research subject, etc. concerning the fact that

measures in accordance with the said withdrawal or refusal will not be taken, along with the reasons, and to obtain understanding of the research subject, etc.

- (i) Withdrawal of all or part of the given consent that the research is commenced or continued;
- (ii) Refusal of all or part of with regard that the research is commenced or continued, based on the information concerning the research, which is notified or made public (including refusal pursuant to the provisions of Part 13.1 (1) B (a) (ii));
- (iii) Refusal of all or part of with regard that the research is commenced or continued, in the course of procedures for obtaining informed consent pursuant to the provisions in Section 5 above; or
- (iv) Refusal by a research subject, concerning the research to which his/her legally acceptable representative has given consent, of all or part of with regard that the research is commenced or continued, in the course of procedures for obtaining informed consent from the said research subjects.

Part 13 Procedures, etc. for Obtaining Informed Consent from Legally Acceptable Representatives, etc.

- 1. Requirements for obtaining informed consent from legally acceptable representatives, etc.
 - (1) When the investigator, etc. or the individual providing existing specimens or information obtains informed consent from a legally acceptable representative, etc. pursuant to the provisions in Part 12 above, all requirements as defined below shall be met.
 - A. The research protocol has description on the following matters:
 - (i) Criteria for selection of legally acceptable representatives, etc.;
 - (ii) Information to be provided to the legally acceptable representative, etc. (including information on (iii) below, when research subjects are those who correspond to either (a) or (b) in B. below); and
 - (iii) When the research subject is an individual who corresponds to either (a) or (b) in B. below, the reason why such an individual shall be the research subject.
 - B. The research subject shall correspond to any of the following:
 - (a) The research subject is a minor. 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, as well as the following matters are prescribed in the research protocol and the chief executive of the research implementing entity approves to carry out the research after relevant ethical review committee deliberation, informed consent shall be obtained not from representative but from the said research subject.

- (i) The research to be implemented does not involve any invasiveness; and
 - (ii) Information concerning implementation of the research, including purpose of the research and how specimens or information will be handled, is made public, and opportunities to refuse that the research is commenced or continued on the research subject are ensured for persons who exercise parental authority over the said research subject and guardians of the minor.
- (b) The research subject is an adult but objectively considered unable to give informed consent.
 - (c) The research subject is a decedent, however, excluding cases in which the implementation of research is against the subject's explicit will expressed during lifetime.
- (2) When obtaining informed consent from legally acceptable representative pursuant to the provisions in Part 12 above, the investigator, etc. or the individual providing existing specimens or information shall select legally acceptable representative, etc. in accordance with the criteria pursuant to the provisions of (1) A. (i) above and provide information to the said legally acceptable representative, etc. pursuant to the provisions in Part 12.3 and of (1) A. (ii) above.
 - (3) When having obtained informed consent from legally acceptable representative, etc., and 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.

2. Procedures, etc. for obtaining informed assent
 - (1) Even when having obtained informed consent from legally acceptable representative but when the research subject is considered to be able to express his/her will concerning the research is to be implemented on him/herself, the investigator, etc. or the individual providing existing specimens or information shall endeavor to obtain informed assent from the said research subject. The same shall not apply to cases in which informed consent is obtained from the research subject pursuant to the provisions of Section 1 (3) above.
 - (2) When carrying out the research for which procedures for obtaining informed assent will be predicted pursuant to the provisions of (1) above, the principal investigator shall, in advance, prescribe information to be provided and the means to provide to research subjects, in the research protocol.
 - (3) When a research subject expresses his/her will of refusal all or part of the research to be commenced or continued, in the course of the procedures for obtaining informed assent pursuant to the provisions of (1) above, the investigator, etc. or the individual providing existing specimens or information shall endeavor to respect such will. This, however, shall not apply when direct benefits to the research subjects' health are expected if the research is commenced or continued and when the legally acceptable representative gives consent to it.

Chapter 6 Personal Information, etc.

Part 14 Basic Obligations about Personal Information, etc.

1. Protection of personal information, etc.
 - (1) With respect to the handling of personal information, investigators, etc. and the chief executive of research implementing entity shall comply with the Act on the Protection of Personal Information (Act No. 57 of 2003), the Act on the Protection of Personal Information Held by Administrative Organs (Act No. 58 of 2003), the Act on the Protection of Personal Information Held by Incorporated Administrative Agencies, etc. (Act No. 59 of 2003) and other ordinances established by local governments in addition to the relevant provisions of these Guidelines.
 - (2) Respecting the dignity of the deceased and the sentiment of the bereaved family, investigators, etc. and the chief executive of research implementing

entity shall handle information about a deceased individual which can identify the specific individual in the same appropriate manner as they handle information about a living individual and take necessary and appropriate measures pursuant to the provisions in Section 2 of this part and in Part 15 below. In addition, they shall endeavor to handle such information appropriately and take relevant measures pursuant to the provisions in Part 16 below.

2. Proper acquisition, etc.
 - (1) Investigators, etc. shall not acquire personal information by deception or other dishonest means when carrying out research.
 - (2) In principle, investigators, etc. shall not handle personal information, etc. acquired in relation with implementation of their research, beyond the scope for which the research subjects have given consent in advance.

Part 15 Security Control Measures

1. Proper handling
 - (1) Investigators, etc. shall appropriately handle the personal information, etc. which has been acquired in relation with implementation of their research and retained by the research implementing entity to which they belong (including information retained by contractor(s) under entrustment agreement; hereinafter referred to the “retained personal information, etc.”) for security control of such information, etc., for the prevention of leakage or loss of or damage and for other security control of the said information.
 - (2) When carrying out research, principal investigator shall instruct and manage investigators, etc. who handle the retained personal information, etc., in cooperation with the chief executive of the research implementing entity he/her belongs to, in order to ensure that such information, etc. will be handled appropriately.
2. Arrangement of systems and supervision, etc. for security control measures
 - (1) The chief executive of research implementing entity shall take necessary and appropriate measures for the prevention of leakage or loss of or damage and for other security control of the retained personal information, etc.

- (2) When the chief executive of research implementing entity has investigators, etc. engaged in the research work at the research implementing entity handle the retained personal information, etc., he/she shall arrange systems and rules necessary for security control of such information and shall exercise necessary and appropriate supervision over such investigators, etc. to ensure the security control of the retained personal information, etc.

Part 16 Disclosure, etc. of Retained Personal Information

1. Public announcement, etc. concerning retained personal information
 - (1) With respect to the personal information acquired in relation with implementation of the research and retained by the research implementing entity (including retained by contractor(s) under entrustment agreement; hereinafter referred to the “retained personal information”), the chief executive of the research implementing entity shall put the matters listed in the following in accessible condition for the specific individuals identified with such personal information (hereinafter referred to as the “person”) or his/her representatives (such condition includes cases in which a response is made without delay at the request of such a person or his/her representative (hereinafter referred to as the “person, etc.”); the same shall apply hereinafter), excepting in case that, with respect to personal information on research subjects, etc., pursuant to the provisions in Part 12 above, the same matters have been informed to them or information on implementation of the research, including how personal information will be handled, have been notified to them or made public.
 - (i) Name of the research implementing entity and name of the chief executive of the research implementing entity;
 - (ii) Purpose of the utilization of the retained personal information, with respect to information utilized in research, a statement to the effect that it is utilized in research (including that it is provided to other research implementing entity(s), if such is the case) and, with respect to information not utilized in research, intended use of such information;
 - (iii) Procedures to meet requests made pursuant to the provisions of (2) of this section or Section 2 (1), (3), (4) or (6) below (hereinafter referred to as “request for disclosure, etc.”) including the amount of

charges, if set pursuant to the provisions of Section 2 (2); and
(iv) The place where consultation, etc. concerning the handling of the retained personal information is undertaken.

(2) When the chief executive of research implementing entity is requested by a person, etc. for notification of the purpose of utilization of such retained personal information as may lead to the identification of the person concerned, the said chief executive shall, without delay, notify to the requesting person, etc. (hereinafter referred to as the “claimant”) of such purpose.

(3) The provisions of (1) (ii) and (2) above shall not apply to any of the following cases:

(i) Cases in which making the purpose of the utilization easily accessible or notifying it to the claimant are likely to harm the life, body, properties and other rights and interests of research subjects, etc. or any other third-party individual(s); or

(ii) Cases in which making the purpose of the utilization easily accessible or notifying it to the claimant are likely to harm the rights or legitimate interests of the research implementing entity.

(4) When the chief executive of research implementing entity has decided not to notify pursuant to the provisions of (3) above, with respect to the purpose of utilization pursuant to the provisions of (2) above, the said chief executive shall, without delay, notify the claimant of that effect. In addition, the said chief executive shall endeavor to explain the reasons and to obtain understanding of the claimant.

2. Response to request for disclosure, etc.

(1) When the chief executive of research implementing entity is requested by a person, etc. to disclose the retained personal information as may lead to the identification of the person (such disclosure also includes notifying the person that the research implementing entity has no such retained personal information as may lead to the identification of the person concerned; the same shall apply hereinafter), the said chief executive shall, without delay, disclose relevant personal information to the claimant. In falling under any of the following, however, the said chief executive may keep all or part of the retained personal information undisclosed. In addition, when any provision has been established in laws or ordinances concerning the

disclosure of the retained personal information, such provisions shall be applied.

- (i) Cases in which disclosure is likely to harm the life, body, property, or other rights and interests of the research subjects, etc. or a third party;
 - (ii) Cases in which disclosure is likely to seriously impede the proper execution of the research work of the research implementing entity; or
 - (iii) Cases in which disclosure violates any laws or ordinances.
- (2) When the chief executive of research implementing entity is requested to notify the purpose of utilization pursuant to the provisions of Section 1 (2) or to make a disclosure pursuant to the provisions of (1) above, the said chief executive may collect charges for taking the measure. In this case, however, the said chief executive shall determine the amount of such charges within the scope considered reasonable in consideration of actual costs.
- (3) When the chief executive of research implementing entity is requested by a person, etc. to correct, add, or delete (hereinafter referred to as “correction, etc.”) such retained personal information as may lead to the identification of the person on the grounds that the retained personal information is contrary to the fact, the said chief executive shall, except in cases in which special procedures are prescribed by any laws and ordinances for such correction, etc., make a necessary investigation without delay within the scope necessary for the achievement of the purpose of utilization and, on the basis of the results, execute relevant correction, etc. of the retained personal information.
- (4) Where the chief executive of research implementing entity is requested by a person to discontinue using or to erase (hereinafter referred to as “discontinuance, etc.”) such retained personal information as may lead to the identification of the person on the grounds that the retained personal information has been acquired against the provisions of Part 14.2 (1) or is being handled against the provisions of Part 14.2 (2), and where it is considered that the request is reasonable, the said chief executive shall execute relevant discontinuance, etc. of the retained personal information, without delay, to the extent necessary to correct such breach of the relevant provisions. This, however, shall not apply to cases in which it is

difficult to execute such discontinuance, etc. of the retained personal information and in which the said chief executive takes necessary alternative measures to protect the rights and interests of the person.

- (5) When the chief executive of research implementing entity has decided not to take all or part of requested measures pursuant to the provisions of (1) above, or has taken all requested measures pursuant to the provisions of (3) or (4) above or decided not to take such measures, the said chief executive shall, without delay, notify to the claimant to that effect (including the content of correction, etc., if any). In addition, when the chief executive of research implementing entity notifies, with respect to all or part of measures requested by a person, etc. pursuant to the provisions of (1), (3) or (4) above, that he/she will not take such measures or will take different measures, the said chief executive shall endeavor to explain the reasons and to obtain understanding of the claimant.
- (6) Where the chief executive of research implementing entity is requested by a person, etc. to discontinue providing to other research implementing entity(s) (including collaborative research implementing entity(s); the same shall apply hereinafter) such specimens or information not anonymized as may lead to the identification of the person on the grounds that the non-anonymized specimens or information are being provided to other research implementing entity against the provisions of Part 12 above, and where it is considered that the request is reasonable, the said chief executive shall, without delay, discontinue providing such specimens or information to other research implementing entity(s). This, however, shall not apply to cases in which it is difficult to discontinue providing such specimens or information to other research implementing entity(s) and in which the said chief executive takes necessary alternative measures to protect rights and interests of the person.
- (7) When the chief executive of research implementing entity has discontinued providing all or part of the non-anonymized specimens or information to other research implementing entity as requested pursuant to the provisions of (6) above, or has decided not to discontinue providing such specimens or information to other research implementing entity, the said chief executive shall, without delay, notify to the claimant to that effect. In addition, when the said chief executive notifies that he/she will not discontinue providing to other research implementing entity, or will

take different measures from discontinuance, the said chief executive shall endeavor to explain the reasons and to obtain understanding of the claimant.

- (8) The chief executive of research implementing entity may determine the following matters on procedures for receiving requests for disclosure, etc. In such case, the said chief executive shall endeavor to mitigate burdens caused on the person, etc. so that the procedures will not impose excessively heavy burdens. In addition, when any person, etc. makes a request for disclosure, etc. not in accordance with relevant procedures, the said chief executive may notify to the claimant that it is difficult to grant such a request for disclosure, etc.
 - (i) The place where requests for disclosure, etc. are to be filed;
 - (ii) The format of the documents (including records made by an electronic method, magnetic method or any other method not recognizable to human senses) to be submitted and other methods of making requests for disclosure, etc. at the time of making request for disclosure, etc.;
 - (iii) Methods of verifying a claimant as the person, etc.; and
 - (iv) Methods of collecting charges, when fees are determined pursuant to the provisions of (2) above.
- (9) The chief executive of research implementing entity may request a person, etc. making a request for disclosure, etc. to show sufficient items to identify the retained personal information in question. In this case, the said chief executive shall provide the information contributing to the identification of the retained personal information in question or other appropriate measures in consideration of the convenience to the person, etc. so that the person, etc. can easily and accurately make a request for disclosure, etc., and take in to consideration that the procedures will not impose excessively heavy burden on the person, etc.

Chapter 7 Response to Serious Adverse Event

Part 17 Response to Serious Adverse Event

1. Response to be made by investigator, etc.

When an investigator, etc. becomes aware of a serious adverse event while carrying out the research which involves any invasiveness, the investigator, etc. shall follow the procedures pursuant to the provisions of Section 3 (1) below,

take relevant measures such as explanation to the research subject, etc. and report to the principal investigator promptly.

2. Response to be made by principal investigator
 - (1) When a principal investigator becomes aware of any serious adverse effect while carrying out the research which involves any invasiveness, the principal investigator shall promptly report to the chief executive of the research implementing entity and take appropriate measures following the operating procedures pursuant to the provisions of Section 3 (1) below. In addition, the principal investigator shall promptly share information on the occurrence of such adverse event with other investigators, etc. engaged in implementing the research.
 - (2) When a principal investigator becomes aware of the occurrence of a serious adverse event while carrying out the research which involves any invasiveness and is being conducted collaboratively with other research implementing entity(s), the principal investigator shall share information on the occurrence of such an event with the principal investigator(s) at the collaborative research implementing entity(s).

3. Response to be made by the chief executive of research implementing entity
 - (1) When carrying out the research which involves any invasiveness, the chief executive of the research implementing entity shall prepare written operating procedures detailing what should be done by the investigators, etc. in response to a serious adverse event and take relevant measures in order that response will be made properly and smoothly in accordance with the said operating procedures.
 - (2) When the chief executive of research implementing entity has received a report from a principal investigator concerning the occurrence of a serious adverse event pursuant to the provisions of Section 2 (1) above, the said chief executive shall make relevant response promptly in accordance with its operating procedures as well as take relevant measures after relevant ethical review committee deliberation to obtain its opinions on the said adverse event.
 - (3) When any unexpected serious adverse event occurs while carrying out 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 said research, the chief executive of the research implementing entity where such an adverse event has occurred shall promptly report to the Minister of Health, Labour and Welfare and make public the status and results of response pursuant to the provisions of (2) above.

Chapter 8 Ensuring of Reliability of Research

Part 18 Managing Conflicts of Interest

- (1) When carrying out research, investigators, etc. shall report to the principal investigator concerning the status of conflicts of interest related to the research such as individual income, etc. and make appropriate response to ensure transparency of such.
- (2) When carrying out the research which may be related to any commercial activity, such as that to confirm the effectiveness or safety of medicine or medical device, the principal investigator shall understand the status of such research-related conflicts of interest and describe it in the research protocol.
- (3) Investigators, etc. shall provide information concerning the status of conflicts of interest described in the research protocol pursuant to the provisions of (2) above, to the research subject, etc. in the course of procedures for obtaining informed consent pursuant to the provisions in Part 12 above.

Part 19 Storage of Specimens and Information, etc. for Research

- (1) Investigators, etc. shall ensure that information utilized in research and records related to such information (hereinafter referred to as “information, etc.”) are accurate.
- (2) When retaining human biological specimens and information, etc., the principal investigator shall prescribe means for storage in the research protocol in accordance with the operating procedures pursuant to the provisions of (3) below, instruct and manage the investigators, etc. to ensure that they retain accurate information, etc. and perform necessary management in order to prevent leakage, mix-up, robbery, loss, etc. of such specimens and information, etc.
- (3) The chief executive of research implementing entity shall prepare written operating procedures for retention of human biological specimens and

information, etc. and exercise necessary supervision in order that such human biological specimens and information, etc. concerning the research carried out by the research implementing entity are retained appropriately.

- (4) The principal investigator shall report to the chief executive of the research implementing entity concerning the management status pursuant to the provisions of (2) above, in accordance with the operating procedures pursuant to the provisions of (3) above.
- (5) The chief executive of research implementing entity shall endeavor to ensure that information, etc. of the research implementing entity will be retained for as long as possible and for research which involves invasiveness (not including minor invasiveness) and intervention, the said chief executive shall exercise necessary supervision to ensure that such information, etc. be retained appropriately at least until five (5) years have passed from the date the end of the research is reported or three (3) years have passed from the date the final publication on the research results is reported, whichever is the later. In addition, the same shall apply to cases in which the research implementing entity retains a decoding index of linkably anonymized information.
- (6) When disposing of human biological specimens and information, etc., the chief executive of the research implementing entity shall exercise necessary supervision to ensure that such human biological specimens and information, etc. have been anonymized.

Part 20 Monitoring and Audit

- (1) The principal investigator shall endeavor to secure the reliability of research and when carrying out research which involves invasiveness (not including minor invasiveness) and intervention, shall perform monitoring and, as necessary, audit, in accordance with the specifications prescribed in the research protocol approved by the chief executive of the research implementing entity.
- (2) The principal investigator shall offer necessary instruction and management to those engaged in monitoring or audit to ensure that such monitoring and audit will be appropriately carried out in accordance with the specifications prescribed in the research protocol approved by the chief executive of the research implementing entity.
- (3) The principal investigator shall not appoint those engaged in implementing

and monitoring of the research, which is subject to the audit, to execute such audit.

- (4) Those engaged in monitoring shall report to the principal investigator concerning results of the said monitoring. In addition, those engaged in audit shall report to the principal investigator and the chief executive of the research implementing entity concerning results of the said audit.
- (5) Those engaged in monitoring and those engaged in audit shall not disclose, without justifiable reason, any information obtained while performing their duties. The same shall apply even after they cease to be engaged in the duties.
- (6) The chief executive of research implementing entity shall support the execution of monitoring and audit pursuant to the provisions of (1) above and take relevant measures for the execution of such monitoring and audit.

Chapter 9 Supplementary Provisions

Part 21 Effective Date

These Guidelines shall come into effect as of April 1, 2015. The provisions in Part 20, however, shall become effective from October 1, 2015.

Part 22 Transitional Measures

- (1) When these Guidelines come into effect, with respect to ongoing research which has been carried out in accordance with provisions of the Ethical Guidelines for Epidemiological Research or the Ethical Guidelines for Clinical Research, prior to the abolition (as of March 31, 2015) of such guidelines, the provisions of such guidelines in force shall remain applicable.
- (2) Prior to these Guidelines come into effect, with respect to ongoing research which has been carried out in accordance with provisions of the Ethical Guidelines for Epidemiological Research or the Ethical Guidelines for Clinical Research, prior to the abolition (as of March 31, 2015) of such guidelines, investigators, etc. and the chief executive of research implementing entity or the organizer of the ethical review committee, respectively, may carry out the said research or operate the ethical review committee in accordance with these Guidelines.

Part 23 Amendment

These Guidelines as a whole shall be reviewed and amended as necessary or when approximately five (5) years have passed after they come into force.