Guidance on the Ethical Guidelines for Life-science and Medical Research Involving Human Subjects

April 16, 2021
(Partially revised on June 6, 2022)

This Guidance explains how to interpret the provisions of the Guidelines and what to consider for specific procedures.

As we are planning to revise this Guidance taking account of feedback from the users, please do not hesitate to submit any comments or make inquiries to the following offices.

The websites listed below also provide links to references used in the seminars on the Ethical Guidelines for Life-science and Medical Research Involving Human Subjects. Please also utilize those materials as references for this Guidance.

[Please direct any comments and inquiries to]

- Office for Bioethics and Biosafety, Life Sciences Division, Research Promotion Bureau, Ministry of Education, Culture, Sports, Science and Technology (MEXT)
  Address: 3-2-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-8959
  TEL: 03-5253-4111
  E-mail: bio-med@mext.go.jp
  Website: MEXT "LifeScience Portalsite" (LIFE SCIENCE NO HIROBA)
  Policies on Bioethics and Safety (the webpage is in Japanese only)
  https://www.lifescience.mext.go.jp/bioethics/seimeikagaku_igaku.html

- Research and Development Division, Health Policy Bureau, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW)
  Address: 1-2-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-8959
  TEL: 03-5253-1111
  E-mail:ethics@mhlw.go.jp
  Website: On Guidelines for Research (the webpage is in Japanese only)
  http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html

- Healthcare Industries Division, Commerce and Service Industry Policy Group Ministry of Economy, Trade and Industry (METI)
  Address: 1-3-1, Kasumigaseki, Chiyoda-ku, Tokyo 100-8916
  TEL: 03-3501-1790
  E-mail: ethics@meti.go.jp
  Website: Personal Genetic Information Guidelines and Bioethics (the webpage is in Japanese only)
  https://www.meti.go.jp/policy/mono_info_service/healthcare/seimeirinri/index.html

[Revision history]
Enactment: April 16, 2021
Revision: June 6, 2022

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Chapter 1 General Provisions
Section 1 Purposes and Basic Policies

The purposes of these Guidelines are, by setting forth matters to be complied with by all persons who are engaged in any processes of life-sciences and medical research involving human subjects, to help them ensure protection of human dignity and human rights and promote appropriate research conduct. All relevant personnel are required to comply with these Guidelines, taking the matters listed below as basic polices in carrying out research:

(i) Conducting socially and academically significant research;
(ii) Ensuring scientific rationality fitting with specific characteristics of the discipline;
(iii) Weighing up possible benefits from research against potential burdens and any other adverse effects on the research subjects;
(iv) Reviewing by an ethics review committee from an independent and fair position;
(v) Providing adequate prior explanation to research subjects and obtaining completely voluntary consent from the research subjects;
(vi) Giving socially vulnerable people special considerations;
(vii) Appropriately managing personal information, etc., which are used in research; and
(viii) Ensuring quality and transparency of research.

1 These Guidelines set forth matters to be complied with by the investigators, heads of research institutions, ethics review committees and any other relevant personnel, regarding, responsibilities of the investigators (Chapter 2), appropriate conduct of research, etc. (Chapter 3), informed consent, etc. (Chapter 4), handling of results, etc. obtained from research (Chapter 5), ensuring credibility of research (Chapter 6), responses to serious adverse events (Chapter 7), ethics review committee (chapter 8), basic responsibilities for personal information, etc., samples and samples/information of a dead person (Chapter 9), etc., primarily aiming at, while assuring human rights protection, safety and well-being of research subjects, ensuring scientific quality and credibility of life-sciences and medical research involving human subjects and outcome thereof as well as ethical validity of the research. These Guidelines apply to all people who are involved in the process of conducting life-sciences and medical research involving human subjects as unified rules.
In addition, besides the provisions of these Guidelines, researchers and personnel equivalent thereto, heads of research institutions, ethics review committees and any other relevant personnel must comply with the Act on the Protection of Personal Information (Act No. 57 of 2003; hereinafter, "APPI") and provisions set forth by the local government. Basic policies (i) to (viii) are the ground rules for research.

2 In (i), the phrase "socially significant research" means research that contributes widely to the maintenance and enhancement of the nation's health and the promotion of patients' recovery from injuries and diseases as well as their quality of life, and thus serves the development of health and welfare of the human being.

3 In (ii), the phrase "scientific rationality fitting with specific characteristics of the discipline" means that the research is conducted in accordance with scientific rules generally accepted in the relevant discipline and based on scientific literature and any other information relating to science and adequate experiments.

4 In (iii), "benefits" mean results or expected blessings which can be obtained from the research. When health benefits are expected on an individual human research subject being involved in the conduct of research, it is a specific blessing for said individual human research subject. At the same time, outcomes of research are general and intangible benefits, having social and academic values.

5 In (iii), a "burden" is used to represent an unfavorable event that occurs definitively on human research subjects in association with the conduct of research, which includes, for example, those associated with "invasion" such as physical or psychological pains, adverse effects on health (including those that are not perceived by the human research subjects), uncomfortable conditions, etc. It also includes time and efforts or financial spending incurred by the human research subjects due to the conduct of research.

6 In (iii), "adverse effects" include a possibility of harm whose actual occurrence due to the conduct of research is uncertain. Examples of such harm include physical or psychological harm, and further, it may even encompass financial or social damages that may be caused due to the conduct of research.

7 In (iii), regarding "weighing up against", first, seek ways to minimize any burden and expected risk on the research subjects while maximizing benefits, and as a result of comprehensive assessment of burdens or risks and benefits, consider the balance between them, such that overall benefits are weighed up against overall expected burdens or risks.

8 In (v), regarding "completely voluntary consent", the investigators who are to obtain informed consent on participation in research must, referring to Principle 27 of the Declaration of Helsinki, be particularly attentive to whether potential research subjects, etc., are in a relationship depending upon the investigators or whether they might be coerced to give consent.
In addition, for the sake of obtaining completely voluntary consent, the investigators should make efforts to promote public or social awareness for better understanding of the research by creating opportunities for that purpose, such as by organizing projects to talk with the general public who may become research subjects in the future.

9 In (vi), the term "socially vulnerable people" means persons who are in a disadvantageous position due to an economic or medical reason, etc., for example, those who lack the capacity to make a decision, and those who are likely to be susceptible to undue influence when making a voluntary decision by anticipating benefits associated with participation in the research or adverse effects that may occur by refusing to participate in the research. The guidelines for good clinical practice (GCP) for the conduct of clinical trials on pharmaceuticals which are agreed in International Conference on Harmonisation (hereinafter, "ICH") of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) describe these people as "vulnerable subjects", which may be referred to, as necessary, wherever appropriate in dealing with specific contents of the research.

10 In (vi), examples of "special considerations" can be, besides hearing of opinions from experts in the ethics review committee according to Section 17-2(4) and

obtaining informed assent according to Section 9-2(1), when disabled persons are selected as the human research subjects, providing explanations suited for a particular disability or using means for aiding communication (such as creating a braille version of the documents for visually impaired persons or using sign language for hearing impaired persons), or, wherever appropriate, providing measures to ensure voluntary decision making by human research subjects (such as presence of an impartial witness). Also, when selecting human research subjects, making a thorough consideration on the necessity of selecting "socially vulnerable people" as the human research subjects is also one way of giving "special considerations".

11 In (vii), an example of "appropriately managing personal information, etc., which are used in research" can be, while giving considerations to the usefulness of personal information, etc., appropriately managing personal information, etc., in order to protect individual's rights and benefits.

Section 2 Definition of Terms

The terms as used herein have the meanings given them below:

(1) Life-sciences and medical research involving human subjects:
Activities which are conducted on humans as the subjects, aimed at the following A or B:

A Obtaining knowledge that contributes to the maintenance and enhancement of the people's health or the patients' recovery from injuries or diseases or quality of life through any of the following means (i), (ii), (iii) and (iv):

(i) understanding of causes of injuries or diseases (including frequency of occurrence and distribution of various different phenomena relating to health as well as factors influential to these);
(ii) understanding of pathologies;
(iii) improving prophylactic methods of injuries or diseases or validation of efficacy; and
(iv) improving diagnostic methods and therapeutic methods in medical practices or validation of efficacy,

B Obtaining knowledge on human genomic and gene structures or functions and mutation or expression of genes, by using samples/information derived from human.

1 Section 2 sets forth definitions of basic terms relating to the objects, subjects, acts, etc., to which these Guidelines apply, thereby defining the scope of application of these Guidelines.

2 "Life-sciences and medical research" includes human genome/gene analysis research (e.g., besides physical anthropology such as human genetics, research using information on human genome and gene in humanities) which aims at elucidating human basic life phenomena (hereditary, generation, immunity, etc.) under the "Ethical Guidelines for Human Genome/Genetic Analysis Research (hereinafter, "Genome Guidelines")" (MEXT/MHLW/METI Public Notice No. 1 of 2001), and also includes medical research (e.g., medical science, clinical medicine and public health, preventive medicine, dentistry, pharmacy, nursing science, rehabilitation medicine, medical technology, medical engineering, and further, studies employing an epidemiological technique using information relating to individual person's health and qualitative studies employing these or these studies employing AI in such fields as care and welfare, food hygienics and dietetics, environmental health and industrial safety and health) under the "Ethical Guidelines on Medical Research Involving Human Subjects (hereinafter, "Medical Guidelines")" (MEXT/MHLW Public Notice No. 1 of 2017).
However, some studies in the field of humanities/social sciences such as medical law and social welfare study may not be included in the "medical research" even if they are associated with medical science, nursing/welfare or the like.

3 The term "human genome and gene" includes, not only human genome and gene which are commonly present in cells forming an individual human and can be passed to progenies (so-called germline mutation or polymorphism), but also genome or gene which only emerge in lesions in an obtained disease such as cancer and are not passed to the next generation (so-called somatic mutation).

4 In the phrase "gene structures or functions and mutation or expression of genes", "structures or functions" and "mutation or expression" include those related to so-called "epigenome" and Omics analysis that studies entire set of molecules and the

like which constitute a living body based on genome information.

5 Research which uses samples/information newly obtained from human research subjects without involving invasion or intervention and research which uses existing samples/information fall under research "involving human subjects".

6 If research only deals with analysis of microorganisms such as bacteria or fungi and viruses isolated from human body, and does not deal with phenomena relating to human health, such research can be determined not to be in the scope of research "involving human subjects".
However, if the research is conducted for the purpose of obtaining knowledge contributing to the maintenance and enhancement of the people's health or the patients' recovery from infectious diseases, etc., through the understanding, etc. of causes and pathologies of the infectious diseases by using information acquired from analysis and/or investigation of pathogenic microorganisms isolated from the patients and by combining said information with other medical information, such research is in the scope of research "involving human subjects".

7 In (1)A(i), the phrase "frequency of occurrence and distribution of various different phenomena relating to health" means various kinds of health indices obtained through epidemiological techniques, for example, occurrence frequency, geographical distribution, gender and age distributions and recovery rates, survival rates, prevalence, healthspan and life expectancy relating to certain kinds of diseases. Examples of "factors influential to these" include daily habit of individual level such as smoking, eating, exercising and sleeping habits, medical services being received by each individual, local environmental and social factors, etc.
The case where influences of taking specific foods and/or nutrients to individual health on human subjects are studied, or the case where influences of behavior modification based on recommendations from a wearable terminal or the like (including those which are not medical devices) on health are studied to obtain medical evaluation are in the scope of "research" as used in these Guidelines.

8 Medical services exclusively for the purpose of prophylaxis, diagnosis or treatment of injuries or diseases are not "research" in the context of these Guidelines. In the case where a medical worker carries out the activities exemplified below, on the outcome or prognosis of his/her patients from such medical services provided by him/herself, if it can be deemed as a part of medical services not for research purposes, such activities can be determined not to be "research" as used in these Guidelines:
- For use as a reference in future medical services, studying cases such as by reviewing medical records or by providing follow-up to patients discharged from the hospital;
- To promote information sharing among medical workers, reporting individual cases (so-called "case reports") in the institution's internal case conferences, study groups with external counterparts or relevant academic conferences outside the institution, professional journals for medical workers, etc.;
- To promote understanding of the existing medical knowledge, etc. among the patients and the general public, publishing on publications, materials for public relations, etc.;
- For self-assessment of medical services as a medical institution, aggregating performances of medical examinations (number of people being diagnosed or treated, outcome of treatment, etc.) during a certain period of time, and showing

them to its medical workers, etc. or including them in a business report, etc.; and
- To ensure quality of medical services provided in the institution (to confirm that standard medical examinations have been provided, prevent hospital infections and accidents in medical services, perform accuracy control of testing, etc.), aggregating and reviewing data available in the institution.

9 "Investigation of the causes of the impairment of workers' health" based on Article 14(1)(ix) of the Ordinance on Industrial Safety and Health (Ministry of Labor (MOL) Ministerial Ordinance No. 32 of 1972) under the Industrial Safety and Health Act (Act No. 57 of 1972) and the "health investigation" according to Article 11 of the Ordinance for Enforcement of School Health and Safety Act (Ministry of Environment (MOE) Ministerial Ordinance No. 18 of 1958) under the School Health and Safety Act (Act No. 56 of 1958) can also be deemed to be a part of business operations which are not for research purposes, and thus can be determined to be not in the scope of "research" as used in these Guidelines.
On the other hand, if samples or data obtained through the business operations are to be used in activities beyond the extent of business operations under said provisions, such activities may be determined as "research" as used in these Guidelines.

10 Regarding healthcare services (such as a health check-up, propagation of recommended lifestyles, etc.) provided locally by local governments, sharing and reviewing a part or all of samples or data taken from, for example, a health check-up among relevant personnel and organizations for accuracy control of said health check-up can also be deemed to be a part of healthcare services, thus, it can be determined that such activities are not in the scope of "research" in the context of these Guidelines.
On the other hand, activities conducted for the purpose of obtaining knowledge contributing to the maintenance and enhancement of the people's health, etc., through understanding pathologies of lifestyle diseases and reviewing validity of prophylactic methods by using information or specimens associated with human health being obtained from healthcare services, such activities are in the scope of "research" as used in these Guidelines.

11 When experiment or training is on scholarly known phenomena such as the case of health training exclusively for education in which acquired samples or data are not to be used for a purpose other than educational purposes, it can be determined to be not in the scope of "research" as used in these Guidelines.

12 A determination whether or not a specific activity falls in the scope of "research" in the context of these Guidelines should be made primarily by the corporation, administrative organ or self-employed individual which carries out said activity, but if such a determination cannot be made easily, it is recommended to seek opinions of the ethics review committee set forth by these Guidelines.

(2) Invasion (invasive):
It means that, due to a method used for a research purpose such as puncture, incision, drug administration, irradiation, questions that touch on psychological trauma, etc., a damage or burden is caused to the physical or emotional state of a human research subject.
Among invasive methods, those that cause a small degree of damage or burden to the physical or emotional state of the human research subject are defined as "minor invasion".

1 Puncture, incision, etc. in medical examination not for research purposes are not involving "invasion" according to the definition of these Guidelines, and if blood, body fluids, tissue, cell, placenta or umbilical cord after delivery, etc. (so-called "residual specimens") being collected in a medical examination not for research purposes is to be used as existing samples/information, it can be determined that such activities do not cause damages or burdens on the bodies of human research subjects (i.e., not involving "invasion").

2 In (2), "drug administration" includes the case where a pharmaceutical product approved based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960; hereinafter, "Pharmaceuticals and Medical Devices Act") (hereinafter, "approved drug") is administered for a research purpose within the extent of said approval. However, even if an approved drug is administered for a research purpose, there may be a case where the administration may be deemed to be not involving "invasion" depending on the ingredients and dose regimen/dosage thereof, etc., because a damage or burden on the physical and emotional state of the human research subjects are extremely small.
In addition, for example, when research is conducted on patients with a certain injury or disease as human research subjects for tracing outcome thereof (prospective studies without undertaking intervention), if a damage or burden is incurred by the subjects due to drug administration in a medical examination not for research purposes, this is not the case of "invasion" defined by these Guidelines.

3 In (2), regarding "irradiation", even when human research subjects are expected to be exposed to similar irradiation in a medical examination not for research purposes, or even when impacts on the human research subjects cannot be measured directly, irradiation which is undertaken for a research purpose by setting certain conditions is deemed to cause a damage or burden on the physical state of human research subjects (i.e., involving "invasion").

4 In (2), "questions that touch on psychological trauma" mean questions relating to a painful experience for a particular individual which is not wanted to be reminded (for example, disaster, accident, abuse, past severe illness or injury, etc.). In addition to such questions, causing a burden in the emotional state of the human research subjects for a research purpose by, for example, an act disturbing emotional stability such as intentionally creating tension, anxiety, etc., also falls in the scope of "invasion".

5 In (2), the phrase "a damage or burden ... to the physical or emotional state of a human research subject" means changes in the stability exceeding the extent that

may be caused at a normal time, any impact on health (including those that are not perceived by the human research subjects) or the like which is caused definitively to the physical or emotional state of a human research subject. Thus, it does not include a possibility of harm whose actual occurrence is uncertain (e.g., risk of causing an adverse event by the administration of a drug for a research purpose, etc.).
The determination of the severity of a damage or burden caused to the emotional state of a human research subject can be made based on emotional distress, etc. which can be generally expected in the population of the human research subjects.

6 In (2), the term "minor invasion" basically corresponds to the term "minimal danger" (which means a danger that does not exceed the limit of possibility of a physical, psychological, social harm to be incurred during daily life or routine medical test, and is of a socially acceptable kind) set forth by the detailed stipulations of the Ethical Guidelines for Epidemiological Studies (MEXT/MHLW Public Notice No. 1 of 2007; hereinafter, "Epidemiological Studies Guidelines") and the Ethical Guidelines for Clinical Studies (MHLW Public Notice No. 415 of 2008; hereinafter, "Clinical Studies Guidelines"), but these Guidelines do not include a possibility of harm whose actual occurrence is uncertain in the scope of "minor invasion" and define it as a damage or burden whose severity is low and which is definitively caused to the physical or emotional state of a human research subject.
Those that are socially acceptable kinds because of low severity of a damage or burden caused in human research subjects, for example, blood sampling or irradiation which causes a damage or burden to the extent (including age and condition of the human subject, frequency of occurrence, etc.) that is generally incurred during blood sampling or chest plain x-ray imaging in a general health examination under the Industrial Safety and Health Act, can be determined as involving "minor invasion".
Also, when puncture, incision, blood sampling or the like takes place in a medical examination not for research purposes, if an additional puncture or incision or amount of blood sampling takes place for a research purpose, if severity of an additional damage or burden caused to the physical or emotional state of the human research subject is very small relative to the puncture, incision, blood sampling, etc. not for research purposes, it may be determined to be "minor invasion".
Besides, for example, when carrying out MRI imaging without using a contrast agent for a research purpose, if possible damages and burdens caused to the physical state of the human research subjects are expected to be small and if there will not be burdens to the physical and emotional states of the human research subjects due to other reasons such as restriction on movements over a long time, it can be determined to be "minor invasion".
In addition, when, for example, a questionnaire survey takes place, if adequate considerations have been given, for example, by explicitly indicating that the survey has a content that causes emotional distress, etc., on human research subjects in advance and allowing them to make a response anonymously or refuse to respond, etc., damages and burdens caused to the emotional state of the human research subjects are considered to be small, thus, it can be determined to be "minor invasion".

7 When determining whether or not an invasion is "minor invasion", it is necessary to make a comprehensive determination taking account of age and conditions of human research subjects, etc. For example, when minors of under age 16 are to be

selected as human research subjects, the determination need to be made carefully, because a damage or burden caused to their physical and emotional states may not be always small.

8 When specific foods and nutrients are to be intaken by human subjects for a research purpose, if eating experiences are sufficiently recognized in the population of the human research subjects, it can be determined that damages and burdens will not be caused to the physical state of the human research subjects (i.e., not involving "invasion").
As for collecting naturally-produced secretions such as urine, stool, sputum, saliva and sweat or fallen hairs or body hairs for a research purpose, or taking surface EMG or ECG measurements or ultrasonic images for a research purpose, if there will not be burdens to the physical and emotional states of the human research subjects due to other reasons such as restriction on movements over a long time, it can be determined to be not involving "invasion".

9 When making a determination whether or not loading a certain kind of exercise stress on human research subjects for a research purpose involves "invasion", and, when it involves "invasion", whether or not the invasion can be deemed to be "minor invasion", it is necessary to make a comprehensive assessment of factors besides contents of the exercise stress, such as criteria for selecting human research subjects, the environment under which the exercise stress is applied, etc.
If changes in the physical stability caused by the exercise stress (such as respiration and pulse increase, sweating, etc.) are relieved in a short period of time by means of taking an appropriate break and water supply, etc., these changes in the physical stability is within the extent of those in the normal time, it may be determined to be not causing damages or burdens to the physical state of the human research subjects (i.e., not involving "invasion"). Also, if activities are those that are socially acceptable kinds as they do not case damages and burdens to the physical or emotional state of the human research subjects, if the exercise stress is around the same level as that of, for example, physical fitness and athletic ability survey conducted by MEXT (new physical fitness test) (including age and condition of the research subjects and occurrence frequency, etc.), it may be determined to be not involving "invasion".

10 When making a determination whether or not each specific research involves "invasion", and, when it involves "invasion", whether or not the invasion can be deemed to be "minor invasion", the above explanations should be referred to as necessary, and, the determination shall be made primarily by the principal investigator in the process of preparing a research protocol, and then be reviewed by the ethics review committee including adequacy of the determination.

(3) Intervention (interventional):
It means an act of controlling the presence and level of factors influential to various different phenomena relating to human health (including activities leading to the maintenance and promotion of health, and drug administration, testing or the like for prophylaxis, diagnosis or treatment of injuries or diseases in medical settings, etc.), for a research purpose (including a medical practice exceeding the extent of ordinary medical examination, which is carried out for a research purpose).

1 In (3), the phrase "various different phenomena relating to human health" means, besides injury or disease states in individual patients, health trends or occurrence trends of certain kinds of diseases in a group of individual persons who have a common attribute (cohort).
Other than the "activities leading to the maintenance and promotion of health" and "drug administration, testing or the like for prophylaxis, diagnosis or treatment of injuries or diseases in medical settings" which are given as examples in these Guidelines, nursing care, lifestyle guidance, nutritional guidance, diet therapy, work therapy, etc., can be examples of factors influential to phenomena relating to human health for which occurrence and level can be controlled. Examples of "activities leading to the maintenance and promotion of health" can be activities and behaviors in daily life such as adequate exercises and sleep, well-balanced meals and quitting smoking.

2 In (3), "control(ling)" means to intentionally make or not to make a change.
An example of intentionally making a change can be giving a sensory stimulation to visual or hearing sense to cause a change in the brain activities or in the psychological state.
Regarding therapeutic methods, diagnostic methods, prophylactic methods for injuries and diseases and any other factors that are considered to be influential to the health of human research subjects, performing a random or non-random allocation (including applying masking or shielding) based on a research protocol is an act of controlling the presence and level of factors influential to phenomena relating to human health for a research purpose, and thus, falls into the scope of "intervention". Allocation includes, besides the case where a population of human research subjects is divided into several groups for comparison between the groups, a case where allocation concerning a specific therapeutic or prophylactic method or any other factors that are considered to be influential to the health of human research subjects is performed on a single group (single arm) without setting a control group.

3 In (3), the term "a medical practice exceeding the extent of ordinary medical examination" means the use of pharmaceutical products (including drugs for *in vitro* diagnosis) or medical devices which are not approved under the Pharmaceuticals and Medical Devices Act (hereinafter, "unapproved drugs or medical devices"), the use of approved drugs or medical devices beyond the scope of approval (dose regimen/dosage, method of use, efficacy/effect or performance), or any other medical practices by means of a novel medical technique, which does not fall in the scope of "specified clinical research" under Article 2(2) of the Clinical Research Act (Act No. 16 of 2017) (hereinafter, "research using an unapproved drug or medical device"). In addition, if a medical practice has already been accepted as medically appropriate conduct and widely practiced, such as when medical insurance

coverage is available, the medical practice can also be determined not to fall in the scope of "a medical practice exceeding the extent of ordinary medical examination". The determination whether or not an activity falls in the scope of "intervention" is made when an act is "a medical practice exceeding the extent of ordinary medical examination, which is carried out for a research purpose", thus, it is not intended to immediately determine that an act which is a medical practice exceeding the extent of ordinary medical examination is "intervention".
The term "medical practice" includes, besides those applied to patients, those applied to healthy human subjects and those carried out not for prophylaxis, diagnosis or treatment of injuries and diseases but for affecting a structure or function of the human body such as those carried out for aesthetic plastic surgery or breast implant, for example. Even if activities do not involve a medical practice exceeding the extent of ordinary medical examination, if the presence and level of factors influential to phenomena relating to human health are controlled for a research purpose, such as by performing random or non-random allocation based on a research protocol, such activities are deemed to be research involving "intervention".

4 An act of continuing for a certain period of time for a research purpose a therapeutic method that has been applied in a medical examination not for research purposes and limiting the patient's choice to receive another therapeutic method is an act of controlling the presence and level of factors influential to the patient's injury or disease state for a research purpose, thus, it falls in the scope of "intervention". On the other hand, for example, if medical information on patients with certain injuries and diseases such as outcome or prognosis thereof is simply collected for a research purpose, without controlling the presence and level of factors such as drug administration and testing for diagnosis and treatment, it may be determined to be not involving "intervention" (observational study), including the case of conducting the activities prospectively.

5 Performing "intervention" may not necessarily involve "invasion". For example, when different cares are carried out prospectively for comparing and reviewing effects, etc., of cares using different methods, such as by performing allocation for reviewing differences between a conventional method and a new method of non-smoking guidance, diet therapy or the like, it generally does not involve "invasion" but falls in the scope of "intervention".

(4) Samples:
It means a part of a human body such as blood, body fluids, tissue, cell and excretions and DNA extracted from these (including those of a dead person) which are used in research.

(5) Information used in research:
It means information relating to human health, such as names of injuries and diseases, drug regimens, results of tests or measurements which have been acquired through diagnosis or treatment of human research subjects, and any other information (including information of a dead person) used in research.

(6) Samples/information:
It means "samples" and "information used in research".

(7) Existing samples/information:
It means samples/information which are either:
(i) Samples/information which exist by the time the research protocol is prepared; or
(ii) Samples/information which are acquired not earlier than the preparation of the research protocol and the purpose of acquisition is not for use in the research pertaining to the research protocol at the time of acquisition.

(8) Genetic information
It means information representing individual's genetic traits and physical constitution, which is acquired through the process of research conducted using samples/information or has already been associated with samples/information and can be passed onto the descendants.

(9) Human research subject:
It means a person (including a dead person) who is either:
(i) A person subjected to the research (including a person asked to be subjected to the research); or
(ii) A person from whom existing samples/information to be used in research have been acquired.

(10) Human research subjects, etc.:
This is a collective reference to both human research subjects and the proxy consenters.

1 In (4), among "samples", whether or not samples which are taken from human body and are used only in analysis of microorganisms such as bacteria or fungi and viruses isolated from human body are in the scope of application of these Guidelines, see explanations of Section 2(1).

2 In (5), "information used in research" does not concern whether or not the information enables to identify a specific individual. It includes information associated with "samples" of (4) and information acquired from analysis of "samples".
In (5), "names of injuries and diseases, drug regimens, results of tests or measurements which have been acquired through diagnosis or treatment of human research subjects" include, besides those recorded in medical records, those described in nursing reports, etc. Also, besides information acquired from human research subjects, it includes, for example, information on phenomena relating to human health which is publicly available through the national demographic dynamics survey, the national health and nutrition examination survey, and the national infection surveillance.

3 In (7), regarding the term "existing samples/information", "(i) Samples/information which exist before the research protocol is prepared" mean those which had already been acquired from human research subjects by the time a research protocol of the research was prepared. It does not matter how or when they were acquired (such as acquired at which institution, or for what purpose).
"(ii) Samples/information which are acquired not earlier than the preparation of the research protocol and the purpose of acquisition is not for use in the research pertaining to the research protocol at the time of acquisition" mean those which are acquired from human research subjects not earlier than the preparation of the research protocol, excluding those which are newly acquired from human research subjects for the purpose of use in the research. Specific examples of this category include:

- Samples/information which are acquired from human research subjects in the research institution for a purpose other than for use in the research (such as for providing medical service or using in another research); and
- Samples/information which were acquired from human research subjects for a purpose other than for use in the research at a place other than the research institution and are provided to the research institution for use in the research.

Note that the term "existing samples/information" as used in these Guidelines can also include samples/information which are acquired from human research subjects not earlier than the preparation of the research protocol. For example, if acquired from a patient (human research subject) for medical services not for research, the samples (so-called "residual specimens") or information (such as medical information in medical records or medical examination data acquired in the process of medical diagnosis and treatment) are classified into (i) if it took place before the preparation of the research protocol, or into (ii) if it took place after the preparation of the research protocol. Thus, in either case, they fall in the scope of the "existing samples/information" as used in these Guidelines. However, before they are used for medical services not for research, if specimens are divided and a portion is used in research, said portion is deemed to be an additional portion acquired for research purposes. An additional portion which is acquired in advance from a patient (human research subject) in the course of medical services not for research purposes and is for use in research later, said portion is not "existing samples/information".
Likewise, when using information or residue samples acquired after preparation of a research protocol through activities exemplified below, such information or residual specimens are "existing samples/information", but an additional portion which is acquired in advance of research and in the course of business operations or activities not for research is not "existing samples/information":

- "Investigation of the causes of the impairment of workers' health" according to Article 14(1)(ix) of the Ordinance on Industrial Safety and Health;
- "Health investigation" according to Article 11 of the Ordinance for Enforcement of the School Health and Safety Act; and
- Healthcare services in the local governments, etc.

<Reference: Categories of "samples/information" in these Guidelines>

Existing samples/information	Samples/information acquired from human research subjects for a purpose other than for the pertinent research (Examples) ➢ Residual specimens, medical records ➢ Samples/information acquired from human research subjects in the conduct of research other than the pertinent research ➢ Genome data acquired by genome analysis of existing samples for

	a purpose other than the purpose of the research.
Samples/information other than the above (samples/information to be newly acquired)	Samples/information to be acquired from human research subjects for use in the pertinent research (Example) ➢ Samples/information to be acquired from patients (human research subjects) during medical services not for research purposes and ahead of the research, as an extra to be used for the purpose of use in research

(11) Research institution
It means any of corporations and administrative organs in which research is conducted and self-employed individuals who conduct research, excluding the case where they are entrusted to undertake only a part of the operations relating to research, such as storing samples/information or performing statistical processing.

(12) Collaborative research institution
It means a research institution in which research is conducted collaboratively based on a research protocol (including a research institution that newly acquires samples/information from human research subjects for said research and provides them to other research institutions).

(13) Research cooperative institution
It means an institution other than research institutions in which research is conducted based on a research protocol, which newly acquires samples/information from research subjects (excluding acquisition of samples involving invasion (excluding minor invasion)) for said research, and only provides the samples/information to research institutions.

(14) Institution conducting the collection and provision of samples/information
It means a research institution which acquires samples/information from research subjects or stores these being provided by other institutions, and undertakes the business of repeatedly and continuously providing these to other research institutions (hereinafter, "collection and provision").

(15) Academic research institutions
This means academic research institutions defined in Article 16(8) of APPI.

(16) Multi-institutional collaborative research
It means research which is conducted in multiple research institutions based on a single research protocol.

1 In (11), "corporations" refer to various kinds of judicial persons under Japanese laws, which include, for example, local government bodies under the Local Autonomy Act (Act No. 67 of 1947), medical corporations under the Medical Service Act (Act No. 205 of 1948), school corporations under the Private School Act (Act No. 270 of 1949), independent administrative corporations under the General Rule Act for Independent Administrative Corporations (Act No. 103 of 1999), national university corporations under the Act of National University Corporations (Act No. 112 of 2003), companies under the Companies Act (Act No. 86 of 2005), general incorporated associations and general incorporated foundations under the Act on General Incorporated Associations and General Incorporated Foundations (Act No. 48 of 2006), etc.
If research is conducted by a voluntary association which is not an incorporated body, the voluntary association or each of the self-employed individuals who participate in the research are the "research institutions" (of note, a voluntary association without the status of corporation is also considered as a "research institution"). In addition, for example, in the case where investigators participating in the research have an affiliation with a corporation or a voluntary association, when the investigators conduct research by using information possessed by the corporation and the voluntary association, both of them are the "research institutions", and the research is considered as a multi-institutional collaborative research in which both of them conduct the research.
Of note, the handling of personal information, pseudonymously processed information or individual-related information in the corporations listed in Appendix 2

of APPI is basically governed by the provisions that apply to the handling of personal information, pseudonymously processed information or individual-related information in the public sector (however, among the provisions of Chapter 5 of APPI, matters relating to personal information files, disclosure, etc., and anonymously processed information are governed by the provisions that apply to administrative organs (see APPI, Article 58(1) and Article 123(2) and (3))). In addition, Japan Organization of Occupational Health and Safety (JOHAS) is one of the "administrative organs", but the handling of personal information, pseudonymously processed information or individual-related information in the hospital service operated by JOHAS is governed by the provisions relating to the handling of personal information, pseudonymously processed information or individual-related information in the public sector (APPI, Article 58(2) and Article 123(1) and (3)).

2 In (11), the term "administrative organs" means administrative organs set forth in Article 2(8) of APPI.

3 In (11), regarding "self-employed individuals", in these Guidelines, when an individual person who is not employed by a corporation nor an administrative organ (such as a physician who works at a medical clinic established as a private practice) carries out research, said person is deemed to be a "research institution" as an self-employed individual who conducts the research.

4 In (11), in the phrase "they are entrusted to undertake only a part of the operations relating to research", what is meant by "they are entrusted" is that another corporation or self-employed individual undertakes by contract to perform a part of the operations relating to research (including the case where temporary workers are caused to perform the operations; the same applies hereinafter).
Besides "storing samples/information or performing statistical processing" exemplified in these Guidelines, operations that can be entrusted may include preparation of the conduct of research (such as procurement of research materials), operations of monitoring and auditing, handling (including providing security control measures) of personal information, etc. being acquired in the course of conducting the research, biochemical analysis of samples, etc.
Whether or not contents of a specific part of operations to be entrusted in research should be decided by the principal investigator in the course of preparing a research protocol, and be described in the research protocol including adequacy of entrustment, as necessary.

5 Excluding the case where a company simply provides research funding and materials, etc. and/or uses results obtained through research and does not engage in the actual practice of research, a company which conducts research (including the case where the research is conducted by entrusting a part of the operation relating to the research or in collaboration with another research institution) generally falls in the scope of "research institutions". Also, when a company participates in research in order to collaboratively conduct the research in medical institutions, universities, etc., such a company may fall in the scope of "collaborative research institution".

6 If a TV program production office or newspaper or journal publisher performs its own activities falling in the scope of "research", it falls in the scope of a "research

institution" as used in these Guidelines. Also, when it gives cooperation to "life-sciences and medical research involving human subjects" conducted by a research institution such as a corporation which runs a university or a company, such a TV program production office or newspaper or journal publisher may fall in the scope of "collaborative research institution" as used in these Guidelines.

7 The national government of Japan, the local governments, etc. may provide funding, facilities, etc., to a medical institution, a corporation being an establisher of a university, etc., as a sponsored project, but, in such cases, the "research institution" is the medical institution or the corporation which receives funding, facilities, etc., to conduct research. An entity which simply uses results obtained through research and do not engage in the actual practice of research is not a "research institution".

8 Since (17) specifies excluding from the "investigators", "a person who newly acquires samples/information and only provides them to a research institution" and "a person who is engaged only in providing existing samples/information" at a place other than research institutions. The institution to which such a person is affiliated is not a "research institution".

9 In (12), regarding "collaborative research institution", an institution to which "a person who is engaged in providing existing samples/information" is affiliated in Section 8-1(3) and an institution which newly acquires samples/information from research subjects based on a research protocol and provides them to other research institutions are not necessarily required to become a collaborative research institution.

10 In (12), "including a research institution that newly acquires samples/information from human research subjects for said research and provides them to other research institutions" intends a case where samples which are acquired while involving minor invasion or greater invasion and provided by a research institution as a collaborative research institution. Other than that, when a research institution newly acquires samples/information involving minor invasion or without involving invasion and provides them to other research institutions, the research institution is not prevented from becoming a collaborative research institution.

11 Note that the provision of Section 8-3(1) applies to a person who is affiliated with (13). Also note that roles of the person are different from those of the person who only provides existing samples/information.
Of note, depending on the contents of research, the person may become a research cooperative institution and a person who only provides existing samples/information. In this case, the person must fulfill the respective roles.

12 In (14), the scope of "institution conducting the collection and provision of samples/information" is not limited to specific research institutions and widely encompasses entities which are operated under the clearly-set objective of ensuring provision of samples/information, such as banks and archives. However, it does not include the case where patients' blood, cells, tissues or the like acquired in a medical institution in association with medical examinations not for research purposes are stored exclusively for use in research conducted by a corporation which runs said medical institution. Also, an institution which does not have a plan to repeatedly and continuously perform the provision to other research institutions at

the time of possessing samples/information is not an "institution conducting the collection and provision of samples/information", but if it does, it is such an institution and is required to comply with the provisions of these Guidelines.

13 In (15), "academic research institutions" are defined in APPI, Article 16(8), as follows:

> APPI, Article 16(8)
> "Academic research institutions" in this Chapter mean a university and other organization or group aimed at academic studies, or a person affiliated thereto.

For interpretation of academic research institutions or applicability thereto, see the Guidelines for the Act on the Protection of Personal Information (hereinafter, "APPI Guidelines") (Common Provisions), 2-18 Academic Research Institutions (Related to Article 16(8) of APPI). Of note, the term "research institution" or "collaborative research institution" as used in the APPI Guidelines may not always correspond to "academic research institutions" defined in APPI. For example, under APPI, a research institution which directly provides medical services to patients at a hospital or clinic is not an "academic research institution". On the other hand, as exemplified by a university hospital, an organization which directly provides medical services to patients as one division of a university corporation that is an academic research institution is considered to be an "academic research institution", because the university corporation as a whole is an organization aimed primarily at "academic studies".
For procedures of obtaining informed consent in medical institutions such as a hospital and a clinic, see explanations of Section 8-1(2)A(c)(I)(ii) and (3)A(b)(III).

(17) Investigators
It means the principal investigator and any other persons who are engaged in the conduct of research (including conduct of operations at an institution conducting the collection and provision of samples/information), excluding a person who is affiliated to a research institution and is:
(i) a person who newly acquires samples/information and only provides them to a research institution;
(ii) a person who is engaged only in providing existing samples/information; or
(iii) a person who is entrusted to be engaged in only a part of the operation relating to research.

(18) Principal investigator
It means a person who is engaged in the conduct of research, and supervises the operations relating to said research in the research institution to which said person is affiliated.
Hereinafter, in the context of multi-institutional collaborative research, the term "principal investigator" is replaced with the representative investigator, as needed.

(19) Representative investigator
It means a principal investigator who represents principal investigators of multiple research institutions in multi-institutional collaborative research.

(20) Head of the research institution
It means the representative of the corporation or the head of the administrative organ in which research is conducted or an self-employed individual who conducts research.

(21) Ethics review committee
It means a collegial body established for conducting inspection or investigation and deliberation from ethical and scientific viewpoints, on matters necessary to determine adequacy of the conduct or continuation of research and any other matters necessary for research.

1 In (17), "any other persons who are engaged in the conduct of research" include co-researchers and employees of the research institution who are engaged in technical assistance or clerical works for research. In addition, a person who is not affiliated to the research institution and is engaged in a part of the operations necessary for obtaining informed consent as stipulated in the Genome Guidelines (hereinafter, "person who assists performance") is also included. The person who assists performance is required to be prohibited to divulge any secret which has come to his/her knowledge in the course of performing his/her duty, by law or by contract. As such, a wide range of persons are encompassed by the "investigators", and each of them is required to fulfill their roles and responsibilities in the research that they are engaged in, based on the provisions of Chapter 2 and thereafter.

2 In (17)(i), "a person who newly acquires samples/information and only provides them to a research institution" means a person who is affiliated to a research cooperative institution and is not involved in research other than by acquiring and providing samples/information.

3 In (17)(ii), "a person who is engaged only in providing existing samples/information" means a person who is not involved in research other than by providing existing samples/information. An example can be a physician, etc., who is employed by a medical institution simply provides a part of medical information possessed by said

medical institution, or a person who is employed by a public health center, etc., simply provides a part of information relating to local residents' health possessed by said public health center, etc., in response to a request made by an investigator who intends to conduct research using said information. On the other hand, when a person in a research institution provides existing samples/information to a collaborative research institution as "a person who is engaged in providing existing samples/information", or when such person is involved in activities other than providing existing samples/information, such as preparing a research protocol or authoring a research paper, the person falls in the definition of "investigators". However, an institution to which "a person who is engaged only in providing existing samples/information" is affiliated is not a research institution.

4 In (17)(iii), "a person who is entrusted to be engaged in only a part of the operation relating to research" means a person who has undertaken a part of the operations relating to research by contract with the research institution (a corporation or self-employed individual who entered into a contractor agreement with the head of the research institution) or a person who is engaged in said operations being undertaken and is not involved in research other than said operations. In this context, "a part of the operation relating to research" which is engaged under entrustment means an operation that does not require direct communication with human research subjects, such as analysis or monitoring.

5 In (18), the "principal investigator" is stipulated as a person who supervises the operations of research that the person is engaged in in the research institution to which the person is affiliated. When multi-institutional collaborative research is to be conducted, whether or not the person has roles and responsibilities in the operations of the research in a collaborative research institution is determined according to the descriptions of a research protocol according to Section 6-1(4) below. Of note, it is not desirable if a single researcher acts as the principal investigator in multiple research institutions in single multi-institutional collaborative research.

6 In (20), regarding the "head of the research institution", when more than one organs within a same corporation are collaboratively involved in the conduct of research, as well, the "research institution" is said corporation, and the "head of the research institution" is the representative of said corporation.

7 In (21), the "ethics review committee" is not limited to that established in the research institution in which the research is conducted, but also includes the one that is established outside the research institution and conducts reviewing upon request of the principal investigator or the like.

(22) Informed consent:
It means completely voluntary consent provided to the investigators or persons who are engaged only in providing existing samples/information by human research subjects, etc., on whether or not the research (including handling of samples/information) is to be conducted or continued, after they have been given adequate information on the objectives, significance and method of the pertinent research, as well as burdens, expected results (including risks and benefits), etc., to the human research subjects, etc., by the investigators or persons who are engaged only in providing existing samples/information and have fully understood such information.

(23) Adequate consent
It means consent under APPI, etc., which is given by an individual human research subject, etc., him/herself on personal information in samples/information, the consent is given by the human research subject, etc., relating to the acquisition or use (including provision) of samples/information after matters necessary for making a decision on the consent have been explicitly provided to the human research subjects, etc., by a reasonable and appropriate method.

(24) Proxy consenter:
It means a person who is considered to be able to represent the will and interests of a living human research subject and is able to give informed consent or adequate consent to the investigators or persons who are engaged only in providing existing samples/information on behalf of the human research subject when the human research subject is objectively determined to be incompetent in giving valid informed consent or adequate consent.

(25) Proxy consenter or the like:
It includes, besides a proxy consenter, a person who is able to provide informed consent or adequate consent when a human research subject is a dead person.

(26) Informed ascent:
It means the process in which a human research subject who is objectively determined to be incompetent in providing valid informed consent expresses his/her assent on research to be conducted or continued, after the human research subject is explained that he/she will be subjected to the research to be conducted or continued in a plain language that can be suitable for and easily understood by the human research subject and has understood the meaning thereof.

1 Regarding difference between (22) "informed consent" and (23) "adequate consent", to obtain the former, it requires to fully explain the matters to be explained according to Section 8-5 and then to obtain consent on the conduct or continuation of the research, whereas the latter can be obtained by explicitly providing the human research subject with matters necessary for making a decision on consent (such as what purpose samples/information are used, withdrawal of consent is possible, etc.) by a reasonable and appropriate method in view of the spirits of APPI and provisions of the local government.
In (23), "matters necessary for making a decision on the consent have been explicitly provided to the human research subjects, etc." are primarily determined by the principal investigator in view of APPI and the provisions of the local government, but the decision and the reason thereof need to be presented to the ethics review committee for review, followed by approval by the head of the research institution.
In (23), examples of the method for obtaining "adequate consent" can be obtaining

verbally expressed consent, receiving a document (including electromagnetic records) or email showing consent, having checked the checkbox of giving consent, having clicked the button of giving consent on the webpage, etc. Of note, however, when research is to be conducted using questionnaire sheets which only describe an overview of the research without providing a field to indicate confirmation that the person gives consent, the fact that such a questionnaire sheet was collected cannot be considered that "adequate consent" was obtained.

2 In (24) and (26), the phrase "objectively determined to be incompetent in giving valid informed consent (or adequate consent)" intends to mean that the person is determined to be as such even in the eyes of persons who do not engage in the conduct of the research, as well.
In addition, it is considered that a determination of whether or not a person has a capacity to give valid informed consent varies depending on the contents of the research to be conducted or continued (such as whether or not there would be any burdens on human research subjects, or whether there are any expected risks and benefits, and contents of these), thus, a same person may be determined to be incompetent to give valid informed consent on one research but competent on another research.

3 In foreign countries, the term "assent" or "informed assent" is often used in cases where children are to be selected as human research subjects. However, these Guidelines set forth that informed assent should be obtained adequately from not only children but also from human research subjects who are objectively determined to be incompetent in providing valid informed consent if they are capable of expressing their will on that they will be subjects of research to be conducted, depending on the degree of incompetency and situations of the human research subjects.

(27) Personal information:
It means personal information defined in Article 2(1) of APPI.
(28) Personal identification code:
It means personal identification code defined in Article 2(2) of APPI.
(29) Special care-required personal information
It means special care-required personal information defined in Article 2(3) of APPI.

1 (27) "personal information" is defined in Article 2(1) of APPI as follows:

APPI, Article 2(1)

"Personal information" in this Act means that information relating to a living individual which falls under any of the following items:

(i) those containing a name, birth date, or other descriptions etc. (meaning any and all matters (excluding an individual identification code) stated, recorded or otherwise expressed using voice, movement or other methods in a document, drawing or electromagnetic record (meaning a record kept in an electromagnetic form (meaning an electronic, magnetic or other forms that cannot be recognized through the human senses; the same applies in the succeeding paragraph, item (ii)); the same applies hereinafter, paragraph (2)); the same applies hereinafter); the same applies hereinafter) whereby a specific individual can be identified (including those which can be readily collated with other information and thereby identify a specific individual)
(ii) those containing an individual identification code

Further, "personal information" is explained in the APPI Guidelines (Common Provisions) as follows:

APPI Guidelines (Common Provisions)

"Personal information" means "information relating to an individual", who is alive, and "those containing a name, birth date, or other descriptions, etc., whereby a specific individual can be identified (including those which can be readily collated with other information and thereby identify a specific individual)" (APPI, Article 2(1)(i)), or "those containing an personal identification code" (Article 2(1)(ii)).

"Information relating to an individual" means, not limited to information identifying an individual such as name, address, sex, birth date, and facial image, but any and all information which represents a fact, decision, evaluation with respect to an attribute of an individual such as the body, properties, occupation and job title, including information which has been publicly available through assessment information, publication, etc., and information in the form of image or audio, either being encrypted or coded for confidentiality or not.

[Case examples of personal information]

Case 1) Full name of the person him/herself.
Case 2) Regarding birth date, contact information (address, domicile, telephone number, email address), company job title or information relating to affiliation, information as a combination of any of these with name.
Case 3) Video information in which the person him/herself can be identified such as information recorded in the security footage.
Case 4) Voice record information from which a specific individual can be identified because name of the person him/herself is included in the record.

Case 5) Information of email address alone from which a specific individual can be identified, such as kojin_ichiro@example.com, as a email address of Mr. Ichiro Kojin whose affiliation is Example Company.
Case 6) Information relating to an individual which was added subsequently to personal information acquired earlier (even if a living specific individual could not be identified at the time it was obtained, if a living specific individual can be identified as a result of subsequent addition of or collation with new information, the information is personal information as from that point).
Case 7) Information from which a specific individual can be identified, which is publicly available by means of an official gazette, phone book, directory of government officials, document with statutory disclosure obligation (such as a financial statement), newspaper, website, social network service (SNS), etc.

2 (28) "personal identification code" is defined in Article 2(2) of APPI as follows:

APPI, Article 2(2)
An "individual identification code" in this Act means those prescribed by cabinet order which are any character, letter, number, symbol or other codes falling under any of the following items:
(i) those able to identify a specific individual that are a character, letter, number, symbol or other codes into which a bodily partial feature of the specific individual has been converted in order to be provided for use by computers
(ii) those character, letter, number, symbol or other codes which are assigned in regard to the use of services provided to an individual or to the purchase of goods sold to an individual, or which are stated or electromagnetically recorded in a card or other document issued to an individual so as to be able to identify a specific user or purchaser, or recipient of issuance by having made said codes differently assigned or, stated or recoded for said user or purchaser, or recipient of issuance

Further, regarding Article 2(2)(i) of APPI, the APPI Guidelines (Common Provisions) explain as follows:

APPI Guidelines (Common Provisions)
"Personal identification code" means any characters, letters, numbers, symbols or other codes which are prescribed by the Cabinet Order to Enforce the Act on the Protection of Personal Information (Cabinet Order No. 507 of 2003; hereinafter, "Cabinet Order") as those able to identify a specific individual from the pertinent information alone, and any information containing those falling into the scope of "personal identification code" is determined to be "personal information".
(omitted)
The Cabinet Order sets forth in Article 1(i) that, among character, letter, number, symbol or other codes produced by having converted any of the bodily features (a) to (g) thereinto so as to be provided for use in computers, "those which conform to standards prescribed by rules of the Personal Information Protection Commission (hereinafter, "PIP Commission") as sufficient to identify a specific individual" fall in the definition of the personal identification code. Said standards are prescribed in Article 2 of the APPI Rules, and those which meet said standards and fall under the category of personal identification code are as follows:

a	A base sequence constituting a deoxyribonucleic acid (i.e., DNA) taken from a cell: Genome data (those expressed by a text string representing a base sequence constituting a deoxyribonucleic acid (i.e., DNA) taken from a cell), which have been made to be able to identify the person him/herself from whom the data were derived, based on the genotype information such as the whole genome sequence data, the whole exome sequence data, the whole genome single nucleotide polymorphism (SNP) data, sequence data consisting of SNPs of at least 40 sites independent of each other, or a sequence consisting of repeats of a unit of four bases of at least 9 loci (short tandem repeat: STR).
b	Appearance decided by facial bone structure and skin color as well as the position and shape of eyes, nose, mouth or other facial elements: Characteristics information sampled from facial bone structure and skin color as well as the position and shape of eyes, nose, mouth or other facial elements, which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition.
c	A linear pattern formed by an iris' surface undulation: Characteristics information sampled from a linear pattern formed by an iris' surface undulation by using an infrared ray or visible right, etc., which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition.
d	Quality of voice decided by vocal cords' vibration, glottis' closing motion as well as the shape of vocal tract and its change when uttering: Characteristics information relating to quality of voice decided by vocal cords' vibration, glottis' closing motion as well as the shape of vocal tract and its change when uttering, which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition, such as a speaker recognition system.
e	Bodily posture and both arms' movements, step size and other physical appearance when walking: Characteristics information sampled from bodily posture and both arms' movements, step size and other physical appearance when walking, which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition
f	Intravenous shape decided by the junctions and endpoints of veins lying under the skin of the inner or outer surface of hands or fingers: Characteristics information sampled from intravenous shape or the like decided by the junctions and endpoints of veins lying under the skin of the inner or outer surface of hands or fingers by using an infrared ray or visible right, etc., which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition.
g	A finger or palm print: (Finger print) Characteristics information sampled from finger print formed by ridgelines on the surface of a finger, which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition. (Palm print) Characteristics information sampled from palm print formed by ridgelines or wrinkles on the surface of a palm, which can be used such that the person him/herself can be recognized by using a device or software aimed at such recognition.

h Combination:
Characteristics information sampled from those listed in Article 1(i)(a) to (h) of the Cabinet Order are combined such that the person him/herself can be recognized by using a device or software aimed at such recognition.

In addition, regarding Article 2(2)(ii) of APPI, the Cabinet Order to Enforce the APPI (Cabinet Order No. 507 of 2003) defines in Article 1(ii) to (viii) as follows:

Cabinet Order, Article 1(ii) to (viii)
(ii) Number of passport set forth in Article 6, paragraph (1), item (i) of the Passport Act (Act No. 267 of 1951)
(iii) Basic pension number set forth in Article 14 of the National Pension Act (Act No. 141 of 1959)
(iv) Number of a driver's license set forth in Article 93, paragraph (1), item (i) of the Road Traffic Act (Act No. 105 of 1960)
(v) Resident record code set forth in Article 7, item (xiii) of the Basic Resident Registration Act (Act No. 81 of 1967)
(vi) Individual number set forth in Article 2, paragraph (5) of the Act on the Use of Numbers to Identify a Specific Individual in the Administrative Procedure (Act No. 27 of 2013)
(vii) Characters, letters, numbers, symbols or other codes prescribed by rules of the Personal Information Protection Commission (hereinafter, "PIP Commission") which are indicated on a certificate set forth in the following in a way to give each person who receives its issuance a different one.
(a) A health insurance card under Article 9, paragraph (2) of the National Health Insurance Act (Act No. 192 of 1958);
(b) An insured person's certificate under Article 54, paragraph (3) of the Act on Assurance of Medical Care for Elderly People (Act No. 80 of 1982)
(c) An insured person's certificate under Article 12, paragraph (3) of the Long-Term Care Insurance Act (Act No. 123 of 1997)
(viii) Any other characters, letters, numbers, symbols or other codes prescribed by rules of the PIP Commission as equivalent to each preceding item.

For detailed definitions of personal identification code, see the APPI Guidelines (Common Provisions).

3 (29) "special care-required personal information" is defined in Article 2(3) of APPI as follows:

APPI, Article 2(3)
"Special care-required personal information" in this Act means personal information comprising a principal's race, creed, social status, medical history, criminal record, fact of having suffered damage by a crime, or other descriptions etc. prescribed by cabinet order as those of which the handling requires special care so as not to cause unjust discrimination, prejudice or other adverse effects to the principal.

Further, "special care-required personal information" is explained in the APPI Guidelines (Common Provisions) as follows:

APPI Guidelines (Common Provisions)
"Special care-required personal information" means personal information comprising the following descriptions (1) to (11), as those of which the handling requires special care so as not to cause unjust discrimination, prejudice or other

adverse effects to the principal.

(omitted)

(1) Race:
This widely covers race, descent or national or ethnic origin. Of note, a simple information of nationality or being a "foreigner" is a legal status, and thus such information alone is not included in race. Also, color of the skin is mere information from which a race may be presumed, and thus is not included in race.

(2) Creed:
This means how a person basically looks at things or how to think, which covers both thought and religious belief.

(3) Social status:
This means a status that is permanently fixed to an individual as his/her own circumstances and cannot be easily escaped therefrom by his/her own efforts during lifetime, which does not include a simple occupational position or academic background.

(4) Medical history:
This means history of the person's past and present medical conditions, and a portion of the information that shows a specific medical history (e.g., a specific individual is affected with cancer, or suffers from schizophrenia).

(5) Criminal history:
This means the fact of previous conviction, in other words, the fact that a person has been convicted guilty by the court and the guilty conviction has become conclusive.

(6) Fact of having suffered damage by a crime:
This means the fact that a person suffers from criminal damage, regardless of a physical, mental or financial damage. Specifically, from among the acts which may constitute structural elements of an offence defined in criminal code, those for which criminal procedures have been commenced.

(7) The fact of having physical disabilities, intellectual disabilities, mental disabilities (including developmental disabilities), or other physical and mental functional disabilities prescribed by rules of the PIP Commission:
This includes information of the following (i) to (iv). Besides, it also includes information which allows to identify the existence of previous existence of the pertinent disabilities (e.g., being a recipient or a former recipient of the welfare service for persons with disabilities based on the Act on Comprehensive Support for Daily and Social Lives of Persons with Disabilities (Act No. 123 of 2005)):

(i) information enabling to identify the existence of "physical disabilities set forth in the Appendix of the Act on the Welfare of Persons with Intellectual Disabilities (Act No. 283 of 1949)";

(ii) information enabling to identify the existence of "intellectual disabilities under the Act on the Welfare of Persons with Intellectual Disabilities (Act No. 37 of 1960)";

(iii) information enabling to identify the existence of "mental disabilities under the Act on Mental Health and Welfare of the Persons with Mental Disabilities (Act No. 123 of 1950) (including developmental disabilities set forth in Article 2(2) of the Act on Support for Persons with Development Disabilities (Act No. 167 of 2004), and excluding intellectual disabilities under the Act on The Welfare of Persons with Intellectual Disabilities)"; and

(iv) information enabling to identify the existence of "a disease without established therapeutic methods or other peculiar diseases of which the severity by those prescribed by cabinet order under Article 4(1) of the Act on Comprehensive Support for Daily and Social Lives of Persons with Disabilities (Act No. 123 of 2005) is equivalent to those prescribed by the Minister of Health, Labor and Welfare under said paragraph".

(8) Results of a health checkup or other examination ("health checkup, etc." in (9)) for the prevention and early detection of a disease conducted on the person him/herself by a medical doctor or other person engaged in duties related to medicine ("doctor or the like" in (9)):
It includes results of a test which determines health conditions of the person him/herself who has undergone the test, such as health examination, health checkup, special health examination and health measurement, stress check, genetic testing (excluding those conducted during medical practices) which are conducted for the purpose of the prevention or early detection of diseases.
Specific examples can be results of a health checkup conducted based on the Industrial Safety and Health Act (Act No. 57 of 1972), results of a stress check conducted based on said Act, results of special health checkup conducted based on the Act on Assurance of Medical Care for Elderly People (Act No. 80 of 1982), etc. In addition, this is not limited to results of health checkups required by law, but also includes results of medical examinations optionally conducted or aided by the insurer or the employer such as a thorough physical examination (so-called "human dock"). Further, it also includes results obtained through a genetic testing conducted without the involvement of a medical institution which determines the person's genotype and the genotype's susceptibility to diseases. However, it does not include a fact that a person received health checkup, etc.
However, it does not include cases when information on personal health such as height, weight, blood pressure, pulse or body temperature is obtained by a method that is not associated with health programs such as health checkup or medical examination or services relating to these.

(9) The fact that guidance for the improvement of the mental and physical conditions, or medical care or prescription has been given to the person him/herself by a doctor or the like based on the results of a medical checkup, etc. or for the reason of disease, injury or any other mental or physical change:
"Fact that guidance for the improvement of the mental and physical conditions has been given to the person him/herself by a doctor or the like based on the results of a medical checkup, etc." includes contents of health guidance, etc., given by a doctor or health nurse to a person who is required to make certain efforts to maintain personal health, as a result of health checkup, etc.
Specific examples of the fact that guidance was conducted can be contents of health guidance conducted by a doctor or health nurse based on the Industrial Safety and Health Act, face-to-face guidance given by a doctor based on said Act, and contents of specific health guidance given by a doctor, health nurse or registered dietitian based on the Act on Assurance of Medical Care for Elderly People. In addition, this is not limited to contents of health guidance required by law, but also includes contents of health

guidance optionally conducted or aided by the insurer or the employer. In addition, it also includes a fact of having received health guidance, etc.
"The fact that medical care has been given to the person him/herself by a doctor or the like based on the results of a medical checkup etc. or for the reason of disease, injury or any other mental or physical changes" means all information on the patient's bodily conditions, medical conditions, therapeutic situations, etc. which could be known to the physician, dentist, pharmacist, clinical nurse or other person who is engaged in medical services in the process of medical care in a hospital, clinic or any other institutions which provide medical services. An example can be medical records. In addition, it also includes the fact of being examined at a hospital, etc.
"The fact that prescription has been given to the person him/herself by a doctor or the like based on the results of a medical checkup etc. or for the reason of disease, injury or any other mental or physical changes" means all information on the patient's bodily conditions, medical conditions, therapeutic situations, etc. which could be known to the pharmacist (including the case where the physician or dentist dispenses medicaments according to a prescription issued by him/herself), in the process of dispensing medicaments in a hospital, clinic, pharmacy or any other institutions which provide medical services. An example can be information described in a drug dispensing record, history of drug intake, drug notebook. In addition, it also includes the fact of having received prescription drugs at a pharmacy, etc. However, it does not include cases where information on personal health such as height, weight, blood pressure, pulse and body temperature is obtained by a method irrelevant to health programs such as health checkup or medical examination or services relating to these.

(10) The fact that an arrest, search, seizure, detention, institution of prosecution or other procedures related to a criminal case have been carried out against the person him/herself as a suspect or defendant (excluding criminal history).

(11) The fact that an investigation, measure for observation and protection, hearing and decision, protective measure or other procedures related to a juvenile protection case have been carried out against the person him/herself as a juvenile delinquent or a person suspected thereof under Article 3(1) of the Juvenile Act (Act No. 168 of 1948).

For details of interpretation of special care-required personal information, also see the APPI Guidelines (Common Provisions) and Q&A regarding the "Guidelines on the Act on the Protection of Personal Information".

(30) Pseudonymously processed information:
It means pseudonymously processed information defined in Article 2(5) of APPI.
(31) Anonymously processed information:
It means anonymously processed information defined in Article 2(6) of APPI.
(32) Individual-related information:
It means Individual-related information defined in Article 2(7) of APPI.
(33) Personal information, etc.
It means personal information, pseudonymously processed information, anonymously processed information and individual-related information.
(34) Deleted information, etc.
It means personal information defined in Article 41(2) of APPI.
(35) Processing method-related information
It means processing method-related information defined in Article 35(i) of the Enforcement Rules for the Act on the Protection of Personal Information (PIP Commission Rule No. 3 of 2016; hereinafter, "APPI Rules").

1 (30) "pseudonymously processed information" is defined in Article 2(5) of APPI as follows:

APPI, Article 2(5)
"Pseudonymously processed information" in this Act means information relating to an individual that can be produced from processing personal information so as not to be able to identify a specific individual unless collated with other information by taking measures prescribed in the following items in accordance with the category of personal information set forth in each said item.
(i) personal information falling under paragraph (1), item (i); Deleting a part of descriptions, etc., contained in said personal information (including replacing said part of descriptions etc. with other descriptions, etc., using a method with no regularity that can restore said part of descriptions etc.)
(ii) personal information falling under paragraph (1), item (ii); Deleting all individual identification codes contained in said personal information (including replacing said individual identification codes with other descriptions, etc., using a method with no regularity that can restore said personal identification codes)

Further, "pseudonymously processed information" is explained in the APPI Guidelines (Pseudonymously/Anonymously Processed Information) as follows:

APPI Guidelines (Pseudonymously/Anonymously Processed Information)
"Pseudonymously processed information" means information relating to an individual, which can be produced from processing personal information so as not to be able to identify a specific individual unless collated with other information by taking the following measures according to the category of the personal information.
(1) (relevant provision number is omitted) When the personal information is of "those containing a name, birth date, or other descriptions, etc., whereby a specific individual can be identified (including those which can be readily collated with other information and thereby identify a specific individual)": Deleting a part of the descriptions, etc., contained in the personal information.
(2) (relevant provision number is omitted) When the personal information is of "those containing an individual identification code":

Deleting all individual identification codes contained in the personal information (if it is still personal information of Article 2(1)(i) of the Act after the deletion, it is necessary to process as personal information of said provision).

"Deleting" includes replacing with other descriptions, etc., using a method with no regularity that can restore "said part of descriptions, etc." or "said personal identification code". "A method with no regularity that can restore" means a method that does not enable restoration of descriptions, etc., or contents before replacement from which a specific individual can be identified from the descriptions, etc., after replacement.

Of note, "a specific individual can be identified" is to see whether or not it can be determined from the information alone or from those stored as a combination of multiple pieces of information in light of common sense, in other words, whether or not identity can be recognized between the information and a living specific person by using the general person's judgement or understanding.

The requirement to be determined as pseudonymously processed information, "not to be able to identify a specific individual unless collated with other information", requires to make the information in such a condition that a specific individual cannot be identified from the processed information *itself*, which does not exclude processed information which has been processed in such a condition that a specific individual can be identified by combining the processed information with other information.

Processing to generate pseudonymously processed information is required to meet the standards prescribed by the Enforcement Rules for APPI under Article 41(1) of APPI.

<Comparison between personal information, pseudonymously processed information and anonymously processed information (image)>

	Personal information	Pseudonymously processed information (personal information)	Anonymously processed information
Adequate processing (required processing level)	-	- Not to be able to identify a specific individual **unless collated with other information**. - **Processed to the extent that enables to identify the person him/herself if it is collated with** the matrix table.	- Not to be able to identify a specific individual, and **not to be able to restore** - **Processed to the extent that the person him/herself cannot be recognized at all**.
Method of processing	-	- Deleting (or replacing) descriptions, etc., from which a specific individual can be identified. - Deleting (or replacing) all personal identification codes. - Deleting (or replacing descriptions, etc., which may cause a property damage if used unjustly.	- Deleting (or replacing) descriptions, etc., from which a specific individual can be identified. - Deleting (or replacing) all personal identification codes. - Deleting codes that link between pieces of information. - Deleting (or replacing)

			specific descriptions. - Other measures taking into consideration the characteristics of personal information database, etc.
Limitation on purpose of use, etc. (Specific purpose of use, limitation on modification)	- Requires to identify the purpose of use. - In principle, the purpose of use cannot be modified without obtaining consent in advance.	- Requires to identify the purpose of use. - Possible to modify the purpose of use. - Under the condition that the person him/herself is not to be identified, or is not to be contacted, etc.	X (Not restricted)
Notice/ publication	- Notifying or making public, etc., of the purpose of use.	- In principle, the purpose of use needs to be notified or made public, if pseudonymously processed information has been acquired or the purpose of use has been modified.	- Making public items of the information relating to an individual to be contained in the anonymously processed information at the time of producing anonymously processed information. - When providing to a third party, making public items of information relating to an individual to be contained in the anonymously processed information to be provided to the third party and the method of provision, in advance.
Rules that apply to the third party provision	In principle, third party provision cannot be made without obtaining consent in advance.	In principle, third party provision is prohibited, but there are exceptions (based on legal provisions, entrustment, succeeding business operation, shared use).	Third party provision is possible. However, there is an obligation of making public.
Prohibition of the act of identifying individuals	X (The act of identifying is not restricted)	O (There is a restriction that prohibits the act of identifying)	O (There is a restriction that prohibits the act of identifying)

2 (31) "anonymously processed information" is defined in Article 2(6) of APPI as follows:

APPI, Article 2(6)

"Anonymously processed information" in this Act means information relating to an individual that can be produced from processing personal information so as neither to be able to identify a specific individual by taking measures prescribed in the following items in accordance with the category of personal information set forth in each of said items nor to be able to restore the personal information.

(i) personal information falling under paragraph (1), item (i): Deleting a part of descriptions etc. contained in said personal information (including replacing

said part of descriptions etc. with other descriptions, etc., using a method with no regularity that can restore said part of descriptions etc.)

(ii) personal information falling under paragraph (1), item (ii): Deleting all individual identification codes contained in said personal information (including replacing said individual identification codes with other descriptions, etc., using a method with no regularity that can restore said personal identification codes)

Further, "anonymously processed information" is explained in the APPI Guidelines (Pseudonymously/Anonymously Processed Information) as follows:

APPI Guidelines (Pseudonymously/Anonymously Processed Information)

"Anonymously processed information" means information relating to an individual that can be produced from processing personal information so as neither to be able to identify a specific individual by taking measures prescribed according to the category of personal information, nor to be able to restore the personal information to reidentify the specific individual.

Processing to generate anonymously processed information is required to meet the standards prescribed by the Enforcement Rules for APPI under Article 43(1) of APPI.

3 (32) "individual-related information" is defined in Article 2(7) of APPI as follows:

APPI, Article 2(7)

"Individual-related information" in this Act means information relating to a living individual which does not fall under any of personal information, pseudonymously processed information and anonymously processed information.

Further, "individual-related information" is explained in the APPI Guidelines (Common Provisions) as follows:

APPI Guidelines (Common Provisions)

"Individual-related information" means information relating to a living individual which does not fall under any of personal information, pseudonymously processed information and anonymously processed information.

"Information relating to an individual" means any and all information which represents a fact, decision, evaluation with respect to an attribute of an individual such as the body, properties, occupation and job title. Among those falling under the "information relating to an individual", name, birth date and other descriptions from which a specific individual can be identified fall under personal information, and thus are not individual-related information. (omitted)

[Case examples of individual-related information]

Case 1) Website view history of an individual which has been collected through a terminal identifier such as Cookies

Case 2) Age, sex, family composition or the like of an individual which are linked to an email address

Case 3) Product purchase history or service use history of an individual

Case 4) Positional information of an individual

Case 5) Information indicating interest or preference of an individual

(*) When information falls into personal information, such information is not

individual-related information. (omitted)

4 (33) "personal information, etc." mean "personal information", "pseudonymously processed information", "anonymously processed information" and "individual-related information" under APPI.

5 (34) "deleted information, etc." are defined in Article 41(2) of APPI as follows:

APPI, Article 41(2) (the underlined part)

A personal information handling business operator, when having produced pseudonymously processed information or having acquired pseudonymously processed information and deleted information etc. (meaning information related to descriptions etc. and individual identification codes that were deleted from personal information that was used to produce the pseudonymously processed information, and, a method of processing carried out pursuant to the provisions of the preceding paragraph; hereinafter the same applies in this Article, and in this Article, paragraph (7), as applied mutatis mutandis pursuant to the following Article, paragraph (3) following the deemed replacement of terms) related to the pseudonymously processed information shall, in accordance with standards prescribed by rules of the PIP Commission as those necessary to prevent the leakage of deleted information etc., take action for the security control of deleted information etc.

(34) "deleted information, etc." include a matrix table of names and provisional IDs, etc., when names or the like of the human research subjects have been replaced with provisional IDs.

6 (35) "processing method-related information" is defined in Article 35(i) of the Enforcement Rules for the Act on the Protection of Personal Information (PIP Commission Rule No. 3 of 2016; hereinafter, "APPI Rules").

APPI Rules, Article 35(i) (the underlined part)

Defining clearly the authority and responsibility of a person handling processing method-related information (which means information relating to descriptions etc., and individual identification codes which were deleted from personal information used to produce anonymously processed information and information relating to a processing method carried out pursuant to the provisions of Article 43(1) (limited to those which can restore the personal information by use of such relating information); the same applies hereinafter in this Article).

<Categories of personal information, etc. in these Guidelines>

<table>
<tr><th colspan="3">Category</th><th colspan="2">Definition</th><th>Examples</th></tr>
<tr><td rowspan="5">Information relating to a living individual</td><td colspan="2" rowspan="3">Personal information (*1)</td><td colspan="2">Those containing a name, birth date, or other descriptions etc., whereby a specific individual can be identified.</td><td>Name, medical information, onymous questionnaire, facial image, etc.</td></tr>
<tr><td colspan="2">Those containing an individual identification code.</td><td>Genome data (*2), insured person's number on a national health insurance card, insured person's symbol or number.</td></tr>
<tr><td rowspan="2">Pseudonymously processed information</td><td rowspan="3">Information relating to an individual that can be produced from processing personal information by a method prescribed by APPI so as <u>not to be able to identify a specific individual unless collated with other information</u>.</td><td>Pseudonymously processed information, which is in a condition that "can be readily collated with other information and thereby identify a specific individual" (such as when keeping personal information based on which pseudonymously processed information was produced, or deleted information, etc., of the pseudonymously processed information).</td><td rowspan="3">See "Pseudonymously/ Anonymously Processed Information: For trustful use and utilization of personal information -Case Examples-" (*3)</td></tr>
<tr><td colspan="2">Pseudonymously processed information</td><td>Pseudonymously processed information, which is not in a condition that "can be readily collated with other information and thereby identify a specific individual".</td></tr>
<tr><td colspan="2">Anonymously processed information</td><td colspan="2">Information relating to an individual that can be produced from processing personal information by a method prescribed by APPI so as neither to be able to identify a specific individual, <u>nor to be able to restore</u> the personal information.</td></tr>
<tr><td colspan="2">Individual-related information</td><td colspan="2">Information which does not fall into any of personal information, pseudonymously processed information and anonymously processed information.</td><td>Website view history, terminal identifiers such as Cookies, genome data which does not fall under the category of genome data.</td></tr>
</table>

*1 Among personal information, those including certain descriptions, etc. (such as disease history, results of health checkups conducted by a doctor or the like, the fact that guidance

or medical service or prescription medicine was provided by a doctor or the like) fall into "special care-required personal information" (see explanations of Section 2(29)). For example, personal information described in medical service records or receipts fall into special care-required personal information.

*2 Genome data means those expressed by a text string representing a base sequence constituting a deoxyribonucleic acid (i.e., DNA) taken from a cell, whereas genome information has medical meaning, such as when genome data falling into the scope of personal identification code are affixed with certain interpretations such as those related to a genetic disease or susceptibility to a disease or information on the selection of therapeutic drugs.

*3 https://www.ppc.go.jp/files/pdf/report_office_zirei2205.pdf

< Classification of MRI or CT images >

An MRI or CT image falls into personal information by itself when a specific individual can be identified from the contents of the image alone, and, when a specific individual can be identified by readily correlated with other information such as name, such a combination with said information as a whole falls into personal information.

Oh the other hand, when it does not fall into personal information, it is individual-related information.

(36) Adverse event:
It means any unfavorable or unintended injury or disease or a sign thereof appeared in human research subjects (including an abnormal laboratory finding), whether or not causation with the research being conducted is established.

(37) Serious adverse event:
It means, among adverse events, an adverse event falling under any of the following categories:
(i) results in death;
(ii) is life-threatening;
(iii) requires inpatient hospitalization or prolongation of existing hospitalization;
(iv) results in persistent or significant disability/incapacity; and
(v) is a congenital anomaly/birth defect on descendent.

(38) Unpredictable serious adverse event:
It means, among serious adverse events, those which are not described in the research protocol or the information sheet, etc. used for informed consent, or, if described, the nature or severity of which is not consistent with the descriptions.

1 In (36), regarding "an abnormal laboratory finding", if a slight deviation from a reference value occurs during normal operations, it may not necessarily fall into the scope of the term "abnormal", but, at the same time, it should be taken as a possible sign of an adverse event.

2 In (37), regarding "serious adverse event", besides those listed as (i) to (v), if there is a serious event that requires measures to prevent occurrence of a situation as listed in (i) to (v), in which, even if it is not life-threatening or will not need hospitalization, human research subjects are exposed to danger a serious event, necessary measures should be provided according to the procedures or manuals, etc. under Section 15-3, and, depending on the contents of research, if there are internationally standardized adverse event assessment criteria, etc. in specific areas of injuries and diseases, said criteria, etc. should be referred to and reflected in the research protocol.

3 In (38), "the research protocol or the information sheet, etc." include, when research uses approved pharmaceuticals or medical devices, a drug package insert of the relevant item.
When research uses unapproved pharmaceuticals or medical devices, a summary of unapproved pharmaceuticals or medical devices to be used in the research (i.e., so-called "investigator's brochure") should be described as a "method of the research" in the descriptions of a research protocol (see Section 7(1)(iv)), and said description in the research protocol may also be taken into account when determining a predictability.

(39) Monitoring:
It means an inspection to be carried out by a person designated by the principal investigator to check the progress of the research and to see whether or not the research has been conducted in compliance with these Guidelines and the research protocol, in order to ensure appropriate conduct of the research.

(40) Audit:
It means an inspection to be carried out by a person designated by the principal investigator to check whether or not the research has been conducted in compliance with these Guidelines and the research protocol, in order to ensure reliability of research results.

(41) Genetic counseling
It means to provide assistance or support to research subjects (proxy consenters) or their blood relatives through rounds of dialogues and information provision making use of the knowledge and counseling techniques on genetic medicine, aiming at eliminating or mitigating possible medical or psychological problems associated with genetic diseases, so that they can make their own choices for their future lives and act accordingly.

1 In (39) and (40), regarding "a person designated by the principal investigator", these Guidelines require that, when multi-institutional collaborative research is conducted, roles and responsibilities of the principal investigators of the collaborative research institutions, respectively, be clarified according to the provision of Section 6-1(4) in a research protocol being drafted, and a representative investigator may give supervision over the collaborative research institutions including designation of persons who are engaged in monitoring or audit in the collaborative research institutions.
In addition, a clear definition of attributes of the person to be designated suffices, and thus a specific individual may not necessarily be designated.

Section 3 Scope of Application of these Guidelines

1 Research to which these Guidelines apply

These Guidelines apply to life-sciences and medical research involving human subjects which is conducted by Japanese investigators or takes place in the territory of Japan. However, in the case where research falls in the scope of application of other guidelines, provisions of these Guidelines apply for matters not stipulated in said other guidelines.

In addition, these Guidelines do not apply to research falling into any of the following categories:

A Research that is undertaken in accordance with legal provisions;

B Research that is subject to standards prescribed by legal provisions; and

C Research that uses only the following samples/information:

(i) samples/information which have a well-established academic value, are widely used in research and are generally obtainable;

(ii) existing information which does not fall into information relating to an individual; and/or

(iii) anonymously processed information which has already been produced.

1 Section 3-1 set forth, among "life-sciences and medical research involving human subjects" defined in Section 2(1), research to which these Guidelines apply or do not apply. The scope of application of these Guidelines includes that of the Medical Guidelines and that of the Genome Guidelines.

These Guidelines are Ethical Guidelines for "life-sciences and medical research involving human subjects", thus, research that does not fall into the definition of "life-sciences and medical research involving human subjects" is not within the scope of application of these Guidelines. However, these Guidelines can still be used as reference to promote adequate conduct of research, depending on the contents of research, for example, when information acquired from human research subjects is used.

2 Regarding the phrase "takes place in the territory of Japan", not only research in which invasion or intervention takes place in Japan, but also research in which neither invasion nor intervention takes place fall into the scope of research that "takes place in the territory of Japan", if samples/information are acquired from human research subjects in Japan or samples/information are provided by an institution in Japan, including the case where analysis, etc. on said samples/information is performed by a foreign research institution outside Japan.

3 Examples of "other guidelines" include:

- Ethical Guidelines on Assisted Reproductive Technology Studies Involving Production of Human Fertilized Embryo
  (MEXT/MHLW Public Notice No. 2 of 2010); and
- Guidelines for Clinical Studies of Gene Therapy, etc.
  (MHLW Public Notice No. 48 of 2019).
- Guidelines for Research Involving the Use of Genetic Information Modification Technologies on Human Fertilized Embryo
  (MEXT/MHLW Public Notice No. 3 of 2019)

For example, when specific research is in the scope of application of other Guidelines, provisions of said Guidelines apply first, and only those that are not stipulated in said Guidelines such as how to handle results obtained from research,

provisions of these Guidelines apply. In addition, if both of the other guidelines and these Guidelines have stipulations on a same matter, provisions of the other guidelines supersede provisions of these Guidelines, even if these Guidelines set forth a higher standard.

4 In A, the "research that is undertaken in accordance with legal provisions" includes, besides registration to the National Cancer Database and the Prefectural Cancer Database based on the Act for the Promotion, etc. of Registration of Cancers (Act No. 111 of 2013; hereinafter, "Cancer Registration Promotion Act"), etc., those for which specific authorities and duties of specific administrative organs, independent administrative corporations, etc. for implementation are specified in legal provisions such as the infection surveillance based on the Act concerning Prevention of Infection of Infectious Diseases and Medical Services for Patients with Infectious Diseases (Act No. 114 of 1998), the national health and nutrition examination survey based on the Health Promotion Act (Act No. 103 of 2002) and obtaining medical information and producing and providing anonymously processed medical information based on the Act on Anonymously processed Medical Data That Are Meant to Contribute to Research and Development in the Medical Field (Act No. 28 of 2017).

5 Under the Epidemiological Studies Guidelines, cancer registration services formerly implemented by local governments were deemed to be healthcare services and thus were excluded from the scope of application of said Guidelines.
The successor system, the Prefectural Cancer Database based on the Cancer Registration Promotion Act, is also defined to be used in research in said Act. However, said Prefectural Cancer Database is implemented by legal provisions, i.e., Cancer Registration Promotion Act. Therefore, said database, including hospitals, etc. which submit disease information to these databases are not in the scope of application of these Guidelines.
Of note, "life-sciences and medical research involving human subjects" which uses information provided by the National Cancer Database and the Prefectural Cancer Database based on the Cancer Registration Promotion Act is in the scope of application of these Guidelines, unless specifically exempted from the application by any of the provisions of A to C.

6 In B, regarding the "research that is subject to standards prescribed by legal provisions", for example, the following standards are prescribed by the Act on Pharmaceuticals and Medical Devices, etc.:

- Ministerial Ordinance concerning Standards for Good Clinical Practice for Pharmaceuticals
  (MHW (Ministry of Health and Welfare) Ministerial Ordinance No. 28 of 1997)
- Ministerial Ordinance concerning Standards for Post-marketing Investigation and Test on Pharmaceuticals
  (MHLW Ministerial Ordinance No. 171 of 2004)
- Ministerial Ordinance concerning Standards for Good Clinical Practice for Medical Devices
  (MHLW Ministerial Ordinance No. 36 of 2005)
- Ministerial Ordinance concerning Standards for Post-marketing Investigation and Test on Medical Devices
  (MHLW Ministerial Ordinance No. 38 of 2005)
- Ministerial Ordinance concerning Standards for Good Clinical Practice for

Products of Regenerative Medicine, etc.
(MHLW Ministerial Ordinance No. 89 of 2014)

- Ministerial Ordinance concerning Standards for Post-marketing Investigation and Test on Products of Regenerative Medicine, etc.
(MHLW Ministerial Ordinance No. 90 of 2014).

These standards apply to clinical trials and post-marketing investigations and tests on pharmaceutical products, medical devices and products of regenerative medicine, etc., controlled under said Act, thus, these Guidelines do not apply. Similarly, as to standards for providing products of regenerative medicine, etc. set forth by the Act for Ensuring Safety, etc. of Regenerative Medicine (Act No. 85 of 2013) (see Ordinance for Enforcement of the Act for Ensuring Safety, etc. of Regenerative Medicine (MHLW Ministerial Ordinance No. 110 of 2014), Articles 4 to 26), these Guidelines do not apply to research in the scope of application of said standards.
Likewise, research in the scope of application of the good clinical research practice (GCRP) provided for in the Clinical Research Act (Articles 8 to 38 of the Enforcement Regulation on the Clinical Research Act (MHLW Ministerial Ordinance No. 17 of 2018)), as well, is not in the scope of application of these Guidelines. In addition, "research that is subject to " means research conducted according to said Act.
However, of note, conduct of clinical research (excluding specified clinical research) under the Act, as well, should be endeavored to meet the GCRP or the like.
Also, if a fundamental statistical survey or a general statistical survey implemented by the procedures set forth by the Statistics Act (Act No. 53 of 2007) fits the definition of "life-sciences and medical research involving human subjects", it may be deemed to be "research that is subject to standards prescribed by legal provisions".

7 In C(i), in the phrase "samples/information which have a well-established academic value are widely used in research and are generally obtainable", what is meant by the phrase "have a well-established academic value" is those which have earned a certain reputation in a peer-reviewed academic paper or relevant academic conference, etc. and have been generally used in major journals without footnotes, or those which have a certain fixed value as generally available samples or information.
As to the "widely used in research", for example, besides information disclosed by the Centers for Disease Control and Prevention (CDC) in the U.S. which is uploaded for download and use in research, information published in peer-reviewed academic papers and original references disclosed by authors, etc. of said papers which are generally available for use in research.
As to the term "samples/information which are generally obtainable", it includes, not limited to those commercially available, those that can be obtained by the investigators if they request a provider organization, for example, HeLa cells and iPS cells established from human-derived cells which are provided as research materials. However, whether or not they are generally obtainable is determined in accordance with legal provisions, etc. in Japan.

8 In C(ii), "information relating to an individual" means personal information, pseudonymously processed information, anonymously processed information, individual-related information and information relating to a dead person equivalent to these (for example, information acquired from an onymous questionnaire survey is

"information relating to an individual", as well). An example of information which is not "information relating to an individual" can be so-called "statistical information" (limited to those for which relationship with a specific individual has been eliminated). Also, "existing information" means (1) information that already exists before the research protocol is prepared, and (2) information which is obtained at the time or after the research protocol was prepared, but it was not for the purpose of use in the research pertaining to said research protocol at the time it was obtained. For interpretation of (1) and (2), see explanations of Section 2(7).

9 In C)(iii), for "anonymously processed information which has already been generated", see the explanation of "8" above.
Of note, even if research is to use anonymously processed information which has already been generated, if samples are used in said research, these Guidelines apply.

2 Information of a dead person These Guidelines apply *mutatis mutandis* to life-sciences and medical research involving human subjects which is undertaken by a research institution in Japan or takes place in the territory of Japan, which involves the handling of information of a dead person.

1 Section 3-2 sets forth application of these Guidelines when research involving the handling of dead person's information is conducted.

2 The term "information of a dead person" refers to information relating to a dead individual person.
In the application of these Guidelines, the term "samples" include samples of a dead person.
Informed consent procedures or the like are presumed to be implemented on a proxy consenter or the like.

3 For the terms relating to samples/information of a dead person or the handling thereof, also see explanations of Sections 2, 8, 9 and 18.

3 Research activities that are conducted outside Japan

(1) When the investigators in Japan conduct research in a place outside Japan (including a case where the research is conducted in collaboration with a research institution abroad), both these Guidelines and the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted must be complied with. However, if standards prescribed by legal provisions of the state or region where the research is conducted provide higher standards than those of these Guidelines, the research shall be conducted in accordance with the standards prescribed by legal provisions of said state or region where the research is conducted in place of the provisions of these Guidelines.

(2) In the case where provisions of these Guidelines set forth higher standards than those of the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted, if there is a situation that makes it difficult to undertake the research in accordance with the provisions of these Guidelines and if the items below are described in the research protocol and the head of the research institution in Japan approves after considering opinions of the ethics review committee concerning said research, the research may be conducted in accordance with the standards prescribed by legal provisions of said state or region where the research is conducted in place of the provisions of these Guidelines:

(i) Appropriate measures will be provided for informed consent; and

(ii) Appropriate measures will be provided for protecting personal information to be used in the research.

1 Section 3-3 sets forth application, etc. of these Guidelines when investigators whose affiliation is a Japanese research institution conduct research in a place outside Japan.

2 In (1), regarding the phrases "provisions of these Guidelines" and "standards prescribed by legal provisions and guidelines of the state or region where the research is conducted", a determination as to which of these Guidelines and standards prescribed by legal provisions and guidelines of the state or region where the research is conducted provide a higher standard must be made on a provision basis. For example, in some cases, provisions regarding the ethics review committee are more strict in these Guidelines than those of the standards of legal provisions and guidelines of the state or region where the research is conducted, but on the other hand, provisions regarding informed consent are less strict in these Guidelines than those of the standards of legal provisions and guidelines of the state or region where the research is conducted. Even if some of the provisions of the state or region where the research is conducted provide a higher standard than those of these Guidelines, if there are other provisions otherwise, research must be conducted in accordance with these Guidelines on that part, while making sure that standards prescribed by legal provisions and guidelines of the state or region where the research is conducted are also complied with. In short, either "provisions of these Guidelines" or "standards prescribed by legal provisions and guidelines of the state or region where the research is conducted" which provide a higher standard will apply.

3 In (1), regarding the phrase "in accordance with the standards prescribed by legal provisions of said state or region where the research is conducted", if standards

prescribed by legal provisions and guidelines of the state or region where the research is conducted require that research be authorized by a national governmental body at the state or region where the research is conducted or reviewed by an ethics review committee or a similar body established in the state or region where the research is conducted in accordance with the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted and the conduct of the research is approved by the head of the research institution of the state or region where the research is conducted, said authorization or approval must be obtained.

4 In (2), the phrase "in the case where provisions of these Guidelines set forth higher standards than those of the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted, if there is a situation that makes it difficult to undertake the research in accordance with the provisions of these Guidelines" is intended to deal with the situation where standards prescribed by legal provisions and guidelines to be observed by the investigators have not been developed adequately mainly in a developing state or region. However, it does not intend to immediately allow application of the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted to the research, simply because provisions of these Guidelines set forth a higher standard than the standards prescribed by legal provisions and guidelines of the state or region where the research is conducted.
For each individual research, a determination that there is a situation that makes it difficult to undertake the research in accordance with the provisions of these Guidelines must be made primarily by the principal investigator when preparing a research protocol, the research protocol including adequacy of such determination must be reviewed by the ethics review committee, and, taking account of the opinions of the ethics review committee, a decision as to whether the research should be approved or refused, etc. must be made by the head of the research institution.
In addition, even if there is a situation that makes it difficult to undertake the research in accordance with the provisions of these Guidelines, if it is possible to conduct the research in accordance with internationally recognized standards such as international ethical guidelines published by the Council for International Organizations of Medical Sciences (CIOMS), etc. it is recommended to conduct the research in accordance with said standards.

5 In (2)(ii), the "personal information to be used in the research" includes both personal information to be newly acquired by the conduct of the research and existing personal information to be used in the research.

Chapter 2 Responsibilities of The Investigators
Section 4 Basic Responsibilities of The Investigators

1 Considerations for human research subjects, etc.

(1) The investigators shall respect life, health and human rights of a human research subject when conducting research.

(2) The investigators shall, regarding the conduct of research, comply with legal provisions, guidelines, etc., and appropriately conduct research in accordance with a research protocol being reviewed by the ethics review committee and approved by the head of the research institution.

(3) The investigators shall, in principle, obtain informed consent in advance of the commencement of research.

(4) The investigators shall appropriately and promptly respond to consultation, inquiry, complaints, etc. (hereinafter "inquiries") brought by human research subjects, etc. and relevant personnel thereof.

(5) The investigators shall not divulge information which has become known to them during their engagement in the conduct of research, without a justifiable reason. This obligation continues even after the investigators no longer engage in the conduct of the research.

(6) The investigators shall endeavor to obtain understanding for the research from a population sharing certain characteristics such as local residents when conducting research that may identify the local residents' own characteristics, by giving explanations of the contents and significance of the research to research subjects, etc. and the local residents, etc.

1 Section 4-1 set forth a basic responsibility of the investigators that they should give consideration to human research subjects, etc. when conducting research.

2 In (2), the term "legal provisions, guidelines, etc." includes voluntary and mandated internal rules and manuals developed by the heads of the research institutions according to Section 5-2.

3 In (3), "in principle" is because there are some cases where procedures to obtain informed consent in advance are not required depending on the contents of research (see Section 8-1, 4, 8 and 9).

4 In (4), "relevant personnel thereof" means persons who are closely involved with human research subjects, etc., such as kin of the human research subjects, etc., besides the proxy consenter or the like.

5 In (5), "information which has become known to them during their engagement in the conduct of research" includes, besides information being obtained from human research subjects for a research purpose, for example, a method and design of research, information or the like concerning originality of the research, etc.

6 In (6), examples of "own characteristics" include genetic traits or those based on environmental factors, social factors, etc. Such characteristics include those that can be identified by studying human genetics using excavated bones, as well as by conducting local cohort study.

7 In (6), an example of "obtain understanding for the research ... by giving explanations of the contents and significance of the research" can be providing

briefing sessions repeatedly to talk with the local residents, keeping on providing information on the research even after the research has been commenced, etc.

2 Education and training
The investigators shall receive education and training regarding research ethics and knowledge necessary for conducting the research, prior to working in the research. Also, they shall continuously receive education and training during the term of the research, as appropriate.

1 The provision of Section 4-2 sets forth education and training should be received by the investigators.

2 Contents of education and training should include, besides various rules for the research which should be generally observed such as ethical guidelines, education and training on misconduct in research activities and COI, etc. relating to research activities. Also, when special skills and knowledge, etc. are required in the conduct of research, education and training on those skills and knowledge, etc. must be received before conducting the research.

3 Examples of various forms of education and training can be workshops held by each of the research institutions and by other organizations (including academic conference, etc.), e-learning, etc.

4 Persons who must receive education and training include persons who are engaged in clerical works for the conduct of research and persons who work as assistants for operations of the investigators. It is not necessary to provide the same, unified contents of education and training to all participants, and it is recommended to arrange to be suitable for the specific contents of the operations.

5 Participants should "continuously receive ... as appropriate", and it is recommended to keep on receiving education and training at least once a year.

6 Since "persons who are entrusted to engage only in a part of the operations relating to research" are not included in the "investigators" under these Guidelines, they may not be necessarily required to receive education and training. However, it may be appropriate to stipulate an obligation of receiving education and training in an agreement with the entrustee depending on the contents, etc. of the operations to be entrusted, as necessary.

Section 5 Responsibilities of the Head of The Research Institution

1 General supervision over research

(1) The head of the research institution shall have the responsibility for providing necessary supervision such that the approved research is conducted adequately.

(2) The head of the research institution shall confirm that the research is appropriately conducted according to these Guidelines and the research protocol, as necessary, and take necessary measures for ensuring appropriate conduct of the research.

(3) The head of the research institution shall ensure that all relevant personnel who are engaged in the conduct of research are well-informed that life, health and human rights of a human research subject must be respected in the conduct of research.

(4) The head of the research institution shall not divulge information which has become known to him/her in the course of performing his/her duties in the institution, without a justifiable reason. This obligation continues even after he/she no longer engages in said duties.

1 Section 5-1 set forth responsibilities of the head of the research institution who is in the position of providing general management and supervision of research to be conducted in said research institution.

2 In (1), "necessary supervision" includes ensuring proper handling of personal information, etc. Of note, in multi-institutional collaborative research, as well, the heads of the research institutions are responsible for the supervision over the proper handling of personal information, etc., in their research institutions, respectively.

3 In (2), examples of "necessary measures" can be responses included in Section 5-2(1) to (6).

4 In (3), the scope of "relevant personnel who are engaged in the conduct of research" includes, similarly to the case of Section 6-5(1), "persons who are entrusted to engage only in a part of the operations of the research" as well as the "investigators".

2 Development, etc., of institutional systems and rules for the conduct of research

(1) The head of the research institution shall develop necessary institutional systems and rules (including matters concerning the handling of samples/information) for the appropriate conduct of research.

(2) The head of the research institution shall, in case of health damages on human research subjects which may occur in research conducted in the research institution, ensure that compensation for the damages and any other necessary measures can be provided appropriately.

(3) The head of the research institution shall take necessary measures for protecting human rights of research subjects, etc. and any people related to them or rights and benefits of the investigators and any people related to them, and ensure that research-related information such as research results will appropriately be made available to the public.

(4) The head of the research institution shall conduct inspection and assessment by him/herself, as necessary, to make sure that research in the research institution complies with these Guidelines, and provide appropriate measures based on the results thereof.

(5) The head of the research institution shall cooperate with inspections and investigations conducted by the ethics review committee.

(6) The head of the research institution shall provide measures for ensuring that the investigators of the research institution receive education and training regarding research ethics and knowledge necessary for conducting the research. Also, the head of the research institution him/herself shall also receive the education and training.

(7) The head of the research institution may delegate powers or duties stipulated in these Guidelines to an appropriate person in the research institution, in accordance with the research institution's internal rules.

1 Section 5-2 sets forth responsibilities of the head of the research institution regarding the development of institutional systems for the appropriate conduct of research that takes place in said research institution and the provision of systems for management and supervision over the investigators.

2 From the perspective of respecting autonomy of academic research institutions such as the respect of university autonomy, when an academic research institution has formulated and published voluntary rules for the proper conduct of research involving the use of personal information either alone or jointly, if the contents of the voluntary rules are appropriate from the perspective of protecting individual rights and benefits and the actual handling thereof comply with the voluntary rules, the PIP Commission shall respect those rules in light of the spirit of Article 146(1) of APPI (see the Guidelines for the Act on the Protection of Personal Information (Common Provisions)). Each research institution falling into "academic research institutions" is expected to prepare its own rules on the proper handling of personal information, etc., in life-science and medical research involving human subjects as a part of such voluntary rules, referring to the provisions of these Guidelines.

3 In (1), the phrase "necessary institutional systems and rules for the appropriate conduct of research" means systems including organizations and personnel necessary for conducting research appropriately based on legal provisions, guidelines, etc. and internal rules and manuals for various kinds of research. Specific examples thereof are listed below. Also, it is important to make internal

rules and manuals being developed known to all the investigators in the research institution. In addition, the term "manuals" means written documents that stipulate standard procedures based on which appropriate conduct of research operations can be maintained constantly:

(a) Formulation of manuals for requesting review by the ethics review committee according to Section 6-2, how to obtain approval of the head of the research institution, etc.
(b) Formulation of manuals for matters, etc. which should be carried out by the investigators in response to a serious adverse event according to Section 15-3;
(c) Development of organizations and systems that can ensure provision of necessary measures for preventing divulgence of information relating to human research subjects, etc.; and
(d) Establishment of an office for receiving inquiry, etc.
(e) When establishing the position of a personal information management officer, policies for selection, operation, etc.

4 In (3), regarding "necessary measures for protecting human rights of research subjects, etc. and any people related to them or rights and benefits of the investigators and any people related to them", when conducting research involving the use of samples/information from which a specific individual can be identified, it is necessary to make it unable to identify a specific human research subject, by deleting name, birth date, address and the like (including replacing with other descriptions, etc., using a method with no regularity that can restore). If it is difficult to do so because of the nature of the disease or symptom or case example, it is necessary to obtain advance consent of the human research subjects, etc.

5 In (4), as for the inspection and evaluation as well as method and timing of performing the same which are to be carried out by the head of the research institution him/herself, the head of the research institution should decide details thereof taking account of the contents, etc. of research to be conducted by the research institution. Also, check sheets for inspection, etc. should be provided by each of the research institutions. When specifying timing of the inspection, etc., frequency thereof (e.g., approximately once a year) shall also be specified.

6 In (5), the "inspections and investigations conducted by the ethics review committee" means inspections and investigations according to Section 17-1(2) or (3).

7 Regarding (6), a person to whom powers and duties of the head of the research institution have been delegated is required to receive education and training necessary for said powers and duties.

8 Based on (7), in accordance with internal rules stipulated by the research institution, powers or duties (such as approving a research protocol, executing a contract with an outside contractor to entrust a part of the operations regarding the conduct of research, making a response to a serious adverse event and providing security control measures for personal information, etc.) may be delegated to an appropriate person who has a sufficient power in the administration of research activities in said research institution (such as the dean of the faculty, the director of the hospital or the president of the facility (e.g., the director of the public health center, the director of the research center)).

Chapter 3 Appropriate Conduct of Research, etc.
Section 6 Procedures concerning Research Protocol

1 Preparation and amendment of a research protocol

(1) The principal investigator shall, when he/she intends to conduct research, prepare a research protocol in advance, and also, when he/she intends to conduct research with contents which are different from those described in a research protocol, amend the research protocol in advance.

(2) The principal investigator shall, when preparing or amending a research protocol of (1), give consideration such that ethical validity and scientific rationality of the research can be ensured, and also, shall make a comprehensive assessment of burdens on human research subjects and expected risks and benefits, and provide measures for minimizing burdens and risks.

(3) The principal investigator who conducts multi-institutional collaborative research shall, for the representation in conducting operations of research to be conducted as the multi-institutional collaborative research, select a representative investigator from among the principal investigators thereof.

(4) The representative investigator shall, when he/she intends to conduct multi-institutional collaborative research, clearly identify the roles and responsibilities of each of the principal investigators of collaborative research institutions and prepare or amend a single research protocol.

(5) The principal investigator shall, when he/she intends to entrust a part of the operations of research, identify the details of the operation to be entrusted and prepare or amend a research protocol.

(6) The principal investigator shall, when entrusting a part of the operations relating to research, execute an agreement in writing or by electromagnetic means (which mean a method using an electronic data processing system or other methods using information and communications technology; the same applies hereinafter) on matters to be complied with by the entrustee and provide necessary and appropriate supervision over the entrustee.

(7) The principal investigator shall, prior to the conduct of invasive (excluding minor invasion) research which involves medical practices beyond the extent of ordinary medical examination, appropriately provide necessary measures such as an insurance coverage for compensating health damages on human research subjects in connection with said research.

1 Section 6-1 sets forth procedures when the principal investigator prepares or amends a research protocol. The principal investigator is required to prepare or amend a research protocol such that ethical validity and scientific rationality of the research are ensured, and obtain approval of the head of the research institution (including approval of amendment; the same applies hereinafter). The investigators are required to conduct the research based on the research protocol approved by the head of the research institution.

2 In (2), the principal investigator must give top priority to ensure safety of the research to be conducted, and, if harm associated with the research is expected and if it is not sure whether safety can be ensured, must decide not to conduct the research (for "burdens on human research subjects", see explanations in Section 1).

3 In (2), "risks" refer to a possibility of harm whose actual occurrence associated with the conduct of research is uncertain,. Examples of such risks include physical and

psychological harms, and further, it may even encompass financial or social harms that may be caused on the human research subjects due to the conduct of the research. In (2), for "benefits", see explanations of Section 1 (iii).

4 In (2), "measures for minimizing burdens and risks" refer to, for example, giving consideration such that samples/information will not be collected from research subjects more than necessary when designing research.

5 In (3), the representative investigator complete formalities such as applying for reviewing by the ethics review committee and sharing information on serious adverse events, as a representative of the principal investigators of the research. How to select the representative investigator and how to divide roles among the principal investigators can be decided by said principal investigator s, but their responsibilities for the research in their own research institutions exist in parallel.

6 In (4), the "roles and responsibilities of each of the principal investigators of collaborative research institutions" must be described as a part of the systems for conducting the research as stipulated in Section 7(1)(ii).
In addition, a single format needs to be used for a single research protocol as a formality of the document describing required information and the consent form. For multi-institutional collaborative research, descriptions on the information given to the research subjects and their consent must be unified among the research institutions, except for the matters unique to each research institution (e.g., name of the principal investigator, contact number of the office receiving inquiry).
When conducting the collection or provision of samples/information as set forth in Section 7(2) for multiple research projects, such research projects should not be treated as a single multi-institutional collaborative research project. A single research protocol needs to be prepared per research project.

7 Regarding (5), the principal investigator is required to prepare or amend a research protocol after defining contents of operations to entrust and a method of supervising the entrustee. Then, they must be described as the descriptions of operations to be entrusted and method for supervising the entrustee of Section 7(1)(xxiii). In addition, the operations to be entrusted as "a part of the operations of research" are those which do not interact directly with research subjects, such as analysis or monitoring.

8 In (5), the contract with the entrustee needs to be executed taking into consideration the contents of the research protocol approved by the head of the research institution. Clerical works for the contract are not necessarily performed by the principal investigator him/herself. The principal investigator may have other people performs the clerical works, but is responsible for confirming the contents of the contract, etc. When entrusting operations in multi-institutional collaborative research, the contract is not necessarily be executed by the representative investigator on behalf of the multiple institutions. Each of the principal investigators may be given the power to execute an individual contract for their institutions, as necessary.

9 In (6), examples of "matters to be complied with by the entrustee" can be security control (e.g., measures similar to those required to the investigators in Section 13) of samples/information to be handled in the operations being entrusted, prohibition of use other than the entrusted use, prohibition of provision of the samples/information to a third party other than the entrustee, confidentiality obligation of information to be

known in the course of performing the operations being entrusted, restriction on a subcontract by the entrustee, obligation to receive education and training, and matters relating to disposal and return of the samples/information at the termination of the contract. The principal investigator is required to actively confirm that provisions of the contract have been observed and the entrustee is not in breach of the contract, besides stipulating matters to be complied with by the entrustee depending on the contents of the operations to be entrusted.

10 In (6), examples of the "necessary and appropriate supervision over the entrustee" may be describing in a contract security control measures which are to be taken by the entrustor as the measures which are required to be taken by the investigators according to Section 18-1 so that said measures or measures equivalent thereto can be taken by the entrustee, along with descriptions of a method for confirming that the measures are taken (e.g., routine onsite inspections) and responses to breach.

11 Regarding (7), an adverse effect caused by the use of an approved pharmaceutical within the extent of said approval may be covered by the Relief System for Sufferers from Adverse Drug Reactions, if the approved pharmaceutical has been used appropriately for the efficacy/effect, dose regimen/dosage, etc. in view of the descriptions of a drug package insert, etc. Therefore, it may be considered that a measure of compensation in case of an adverse effect has already been provided. In addition, it is important to note that whether or not compensation under said Relief System is issued is determined based on the results of deliberation of a working group of MHLW after a petition for issuance of compensation has been submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), and there are some exclusions from the Relief System.

12 Regarding (7), for specific guidance on the contents of compensation, it may be helpful to refer to the "Guidelines on Compensation for Health Damage on Human Research Subjects" published on December 25, 2018 by Japan Pharmaceutical Industry Legal Affairs Association (*IHOKEN*) which are considered to have certain achievements in the field of clinical trials.

13 Regarding (7), measures for compensation for a health damage incurred by a human research subject may not be necessarily limited to the payment of money based on the insurance coverage. For example, a medical agent or the like that is expected to cause a serious adverse effect with high frequency may not be completely compatible with the idea of compensation by insurance, and there may not be no insurance product that can compensate possible health damages caused by such medical agent. However, even in such cases, substantial compensation can be provided by other means, such as provision of medical services, etc. suitable for the characteristics of the medical agent to be used in the research.
Decisions whether to provide a monetary compensation and, when providing, to what extent the compensation is allowable should be made by the principal investigator on a case basis depending on the contents of the research protocol while taking account of the kind of the pharmaceutical product or medical device used in the research, characteristics of the disease, burdens on human research subjects and expected risks and benefits, etc. It is considered to be a minimal prerequisite that this aspect is also reviewed by the ethics review committee and then explained in writing to the human research subjects with specific details and consent is obtained in writing.

2 Request for review by the ethics review committee

(1) The principal investigator shall seek opinions of the ethics review committee as to whether or not research can be conducted.

(2) The representative investigator shall, in principle, ask for a comprehensive review by a single ethics review committee with respect to a research protocol for multi-institutional collaborative research.

(3) The principal investigator shall, after seeking opinions of the ethics review committee, submit results thereof and documents submitted to the ethics review committee, and any other documents requested by the head of the research institution to said head of the research institution, and obtain approval for the conduct of the research in the research institution.

(4) Notwithstanding the provisions of (1) to (3), when it is determined to be necessary to urgently conduct research in order to prevent the occurrence or spread of a hazard to public health, the principal investigator may conduct the research based on the approval of the head of the research institution alone, before seeking opinions of the ethics review committee as to whether the research can be conducted. In this case, however, the principal investigator shall seek opinions of the ethics review committee upon receipt of the approval without delay, and, if the ethics review committee gives opinions that the research should be suspended or discontinued or the research protocol should be amended, shall respect said opinions and respond appropriately such as by suspending or discontinuing the research or amending the research protocol.

(5) The principal investigator shall, when seek opinions of individual ethics review committee for multi-institutional collaborative research not according to (2) above, also provide the ethics review committee with necessary information for the review, such as statuses relating to the approval of the conduct of research and results of review by other ethics review committees and progress of the research.

1 Section 6-2 sets forth procedures that the head of the research institution is required to comply with, such as seeking opinions of the ethics review committee before making a decision as to whether or not research is approved to conduct.

2 Regarding (1), it is not intended to allow the principal investigator to seek opinions of a different ethics review committee only on the amendment after commencing research. Such a different ethics review committee does not have knowledge on the details of the research or the reviewing in the past, because of which it is not possible to conduct adequate reviewing. Thus, opinions must be requested to the same ethics review committee as that conducted the initial review of the research.

3 In (2), when the representative investigator requests reviewing to an ethics review committee, it is necessary to take certain steps such as making an arrangement with relevant research institution in advance of requesting the review. In this case, since systems for conducting research in the research institution are also reviewed in accordance with Section 17-4(1), information on said systems must also be provided. In addition, if a research institution intends to join as a collaborative research institution in research which has already been commenced, the research institution is required to additionally seek opinions of the same ethics review committee for the collaborative part of the research.
However, it is also possible to seek opinions of the ethics review committee of its institution, rather than requesting comprehensive review by the ethics review

committee of the collaborative research institution, taking account of specific situations of each research institution.

4 In (3), when comprehensive review is conducted, the representative investigator is required to share results of the review, records of the review which clarify the reviewing process and attendance of the members of the ethics review committee with the principal investigator of the collaborative research institution, and, based thereon, the principal investigator of each research institution must obtain approval of the head of the research institution to conduct the research.
However, it is not considered that the representative investigator is required to request review once again at a collaborative research institution which is different from the one to which the representative investigator is affiliated.

5 In (4), the phrase "when the head of the research institution finds that it is necessity to conduct the research immediately in order to prevent the occurrence or spread of a hazard to public health" is intended to apply to a situation where there is no time to seek opinions of the ethics review committee due to an impending threats of occurrence or spread of a hazard to public health such as an infectious disease. In addition, even if research is approved to conduct before seeking opinions of the ethics review committee, the informed consent procedures must be completed based on Section 8.

6 In (4), "without delay" intends to mean without causing an unreasonable delay.

7 In (2) and (5), the principal investigator and the representative investigator need to have thorough discussion between their counterparts to decide the method of reviewing (comprehensive review or individual review), while taking account of the systems in the research institutions, details of the research, etc.

8 In (5), examples of the "necessary information for the review" can be such information as results of review which had been conducted by another ethics review committee, status of approval in the collaborative research institution (including process of the review, and conditions, etc. attached to the approval), progress of research which has been conducted in the collaborative research institution. As for the scope and extent of "necessary information for the review", they need to be determined suitably, taking into consideration the contents of each individual research, etc.

9 When requesting review by an ethics review committee of research as multi-institutional collaborative research, "review by a single ethics review committee", and "review by ethics review committees" may be co-existed.

3 Approval, etc. by the head of the research institution

(1) The head of the research institution shall, when requested by the principal investigator for approval of conducting research, decide to give or not to give approval to conduct research and any other necessary measures for the research, while respecting opinions of the ethics review committee. In this case, when the ethics review committee gives opinions that the conduct of the research is inappropriate, the head of the research institution shall not give approval to the conduct of the research.

(2) The head of the research institution shall, upon knowing any fact or obtaining information which is considered to be influential to continuance of research conducted in the research institution, promptly make necessary responses such as suspending the research or investigating the cause, as needed.

(3) The head of the research institution shall, upon knowing any fact or obtaining information which undermines may undermine integrity of the conduct of research or credibility of research results, promptly take necessary measures.

1 Section 6-3 set forth that the head of the research institution is required to respect opinions of the ethics review committee, when deciding necessary measures such as issuance of approval to conduct the research.

2 Regarding (1), the head of the research institution must review whether to give or not to give approval of research from the standpoint whether or not the own institution has institutional system for adequately conduct the research, etc., and notify the results in writing. The same applies to the case where there is any change in the research protocol. "Any other measures necessary for the research" mean instructions such as conditions attached to the approval to conduct research, amendment of a research protocol and discontinuation of research.

3 In (2), the scope of "upon knowing any fact or obtaining information which is considered to be influential to continuance of research conducted in the research institution" includes, besides those being reported by the principal investigator according to Section 11-2(2) or (3) and those being directly reported by the investigators according to Section 11-1(2), those being reported by a whistleblower, etc. who are not affiliated to the research institution. Specific examples can be, taking also into account the characteristics, etc. of the research, when there is a serious deviation from the research protocol being approved by the head of the research institution, a falsification or fabrication of information, data, etc. has been found, when an overall assessment of burdens on human research subjects and expected risks and benefits to be incurred by human research subjects is likely to be changed due to occurrence of a serious adverse event, etc., when procedures of informed consent, etc. are not followed adequately, and when there is divulgence of personal information, etc.

4 In (3), a fact or information that undermines "integrity of the conduct of research" means, in the conduct of the research, a fact or information of such as deviation from the selection policies of human research subjects or research methods based on the research protocol. Also, a fact or information "that undermines credibility of research results" means a fact or information such as falsification or fabrication of research data. Further, "information that may undermine " means information that has not been determined to be a definite fact since such contents were known.

5 In (3), examples of "necessary measures" include, besides confirming factual evidence on matters being reported and, where necessary, requesting suspension or discontinuation of the research based on the facts and information being confirmed and responding to human research subjects, providing necessary and appropriate measures for preventing any adverse effects incurred by the investigators, whistleblowers, etc. who have made the report which initiated the situation.

6 For the understanding of (3), also see the "Guidelines for Providing Appropriate Responses to Misconduct in Research Activities" (Decision of August 26, 2014 by the Minister of Education, Culture, Sports, Science and Technology) and the "Guidelines for Providing Appropriate Responses to Misconduct in Research Activities in The Fields of Health, Labour and Welfare" (Ka-Hatsu 0116 No. 1 of January 16, 2015, Decision by the Chief of the Health Science Division of the Minister of Health, Labour and Welfare (Last revised: February 23, 2017)).

4 Registration of summary of research

(1) The principal investigator shall, for research involving intervention, prior to the conduct of the research, register a summary of the research to an open database such as database organized by MHLW (Japan Registry of Clinical Trials: jRCT), and promptly update it according to the amendment of the research protocol and the progress of the research. In addition, for research other than the foregoing, the principal investigator shall endeavor to register a summary of the research, and promptly update the information in accordance with any amendment of the research protocol and the progress of the research.

(2) In the registration of (1), however, this does not apply to matters that have been approved by the head of the research institution based on opinions of the ethics review committee as those that are necessary to be kept undisclosed for the protection of human rights of human research subjects, etc., and people relevant thereto or rights and benefits of the investigators and people relevant thereto.

1 Section 6-4(1) sets forth registration of a summary and progresses of research. For research involving intervention, to prevent a situation where only research results convenient for the investigators are disclosed despite the fact that the intervention is made for the research, a summary of research must be registered to an open database in advance, and, for the purpose of ensuring transparency in the process of conducting research, progress of the research must also be registered.

2 Contents to be registered as a summary of research can be name, purpose and method of the research, institutional systems for conducting the research and policies on the selection of human research subjects. When multi-institutional collaborative research is to be conducted, in accordance with the roles prescribed in the research protocol, the representative investigator may take charge of the registration. In that case, it is important to note that information on all collaborative research institutions participating in the research must be registered. In addition, registration must be completed before the commencement of the period of research described in the research protocol approved by the head of the research institution.

3 In (2), "however, this does not apply" means that some contents are not required to register, if nondisclosure is approved by the head of the research institution based on opinions of the ethics review committee that the nondisclosure is reasonable from the standpoint of protecting information that may cause unreasonable damage to an individual person's rights and benefits, intellectual properties, etc. Except said contents, registration and update of a summary of research are required.

4 To enable comprehensive information search, it is necessary to register in any of the open databases established by the National University Hospital Council of Japan, including jRCT. All of these databases can be comprehensively searched on the website of the National Institute of Public Health. Whether to additionally register to an open database in a foreign state may be decided by each research institution.

- jRCT (Japan Registry of Clinical Trials)
  https://jrct.niph.go.jp/
- University Hospital Medical Information Network Center Clinical Trials Registry (UMIN-CTR)
  https://www.umin.ac.jp/ctr/index-j.htm
- Website of the National Institute of Public Health
  https://rctportal.niph.go.jp/

5 Ensuring appropriate conduct of research

(1) The principal investigator shall instruct and manage the investigators who are engaged in the conduct of the research and any other relevant personnel such that the research will be conducted adequately in accordance with a research protocol and the credibility of research results will be ensured.

(2) The principal investigator shall, in the conduct of invasive research, when they become aware that a serious adverse event has occurred, promptly provide necessary measures.

1 In (1), "the investigators who are engaged in the conduct of the research and any other relevant personnel" include, besides the investigators including staff members who are engaged in works of technical assistance or clerical works in the research institution, persons who are entrusted to engage only in a part of the operations relating to research.

2 In (1), regarding "the research will be conducted adequately", the principal investigator is required to manage acts of the persons engaged in the research, and make sure that they are adequate in light of these Guidelines and comply with the research protocol. On the other hand, if any inadequate acts have come to the knowledge of the principal investigator, he/she must report thereof to the head of the research institution on whether the acts do not comply with these Guidelines, or are deviation from the research protocol, etc.

3 In (2), for "necessary measures", see explanations of Section 15-2.

6 Post-research procedures

(1) The principal investigator shall, upon completion (including discontinuation; the same applies hereinafter) of research, report thereof, in writing or by electromagnetic means, to the ethics review committee and the head of the research institution with a summary of research results, without delay.

(2) The principal investigator shall, upon completion of research, make public the results of the research without delay, after providing measures necessary for the protection of human rights of human research subjects, etc. and people relevant thereto or rights or interests of the investigators and people relevant thereto. Also, the principal investigator shall, regarding invasive (excluding minor invasion) research involving intervention, when the final publication of the results has been made, report thereof to the head of the research institution without delay.

(3) The principal investigator shall, upon completion of research involving intervention, register results of the research results without delay, to the open database to which a summary of the research was registered according to Section 4(1). In addition, for research other than the foregoing, the principal investigator shall endeavor to register results of the research.

(4) The principal investigator shall, when research involving medical practices beyond the extent of ordinary medical examination have been conducted, endeavor to ensure that human research subjects can receive the best prophylaxis, diagnosis and treatment obtained from the results of the research, even after completion of the research.

1 Section 6-6 sets forth procedures after completion of research. The term "upon completion of research" includes, besides when the research period described in the research protocol has been expired, when the research has been discontinued and there is no prospect of resuming.

2 In (1), the report without delay should be made roughly within three months from the completion of the research.

3 (2) sets forth publication of research results. In the Genome Guidelines, publication of research results was one of the exemplified means for ensuring transparency of research, which is one of the obligations of the investigators. These Guidelines, however, require publication of research results of all research projects to which these Guidelines apply, from the standpoint of ensuring transparency of research.

4 In (2) and (3), the term "without delay" intends to mean without causing an unreasonable delay. However, an institution which has performed only the provision of existing samples/information and a research cooperative institution are not required to publish research results.

5 Examples of a method of publishing the results can be presentation in an academic conference, publication of an article on an academic journal and registration (including the registration of a summary and results of research of subsections 4 and 6 above) to an open database. Methods are not necessarily limited to these, however, a method that is viewable only by limited people cannot be considered appropriate. Therefore, each research institution is required to make an appropriate decision on what method is appropriate as a method of publication, taking account of the required descriptions of a research protocol (see Section 7(1)(xiii)). In

addition, publication of the results is required not only when an expected results have been obtained but also when an expected results have not been obtained.

6 In (2), for "measures necessary for the protection of human rights of human research subjects, etc. and people relevant thereto or rights or interests of the investigators and people relevant thereto", see explanations of Section 5-2(3).

7 The term "final publication" means when there is no prospect of further publication than the publications that had been made by that time. After making a report that the final publication has been made, if there arises a need of publishing the results of research, a report thereof must be made to the head of the research institution promptly.

8 Regarding (4), the principal investigator who has conducted research involving a medical practice exceeding the extent of ordinary medical examination should endeavor to ensure that human research subjects can receive the best prophylaxis, diagnosis and treatment obtained from the results of the research, even after the conduct of the research has been completed on the human research subjects. In particular, when the human research subjects make a decision whether to receive the treatment, etc., after being participated in the research using an unapproved drug or medical device, the principal investigator must explain to the human research subjects, etc. financial burdens, etc. which may be needed to continue the treatment, etc., besides knowledge being obtained from the results of the conduct of the research.

Section 7 Descriptions of Research Protocol

(1) Matters to be described in a research protocol (excluding the case falling under (2)) shall be as given below, in principle; provided, however, that this does not apply to matters that have been approved by the head of the research institution upon consideration of opinions of the ethics review committee:

(i) Title of the research

(ii) Institutional system to carry out the research (including names of all research institutions and research cooperative institutions, names of the investigators, and name of the person who only provides existing samples/information and name of the institution as affiliation of said person)

(iii) Objectives and significance of the research

(iv) Method and period of the research

(v) Policies on selection of human research subjects

(vi) Scientific rationale of the research

(vii) Procedures, etc. for obtaining informed consent according to Section 8 (including matters concerning explanation and consent according to said section, if informed consent is received)

(viii) Handling of personal information, etc. (including the method of processing if it is to be processed, and the description of preparing pseudonymously processed information and anonymously processed information if such information is to be prepared)

(ix) Burdens on human research subjects and expected risks and benefits, and a comprehensive assessment thereof, and measures for minimizing the burdens and risks

(x) Method of storing and disposing of samples/information (including references relating to information to be used in research)

(xi) Contents and method of reporting to the head of the research institution

(xii) Sources of research funding and any other situations relating to conflict of interest of the research institution regarding the research, and personal incomes and any other situations relating to conflict of interest of the investigators regarding the research

(xiii) Method of disclosing information relating to the research

(xiv) Handling of results and the like obtained from the research

(xv) Systems for allowing human research subjects, etc. and people relevant thereto to make inquiries regarding the research and a point of contact for inquiries (including genetic counseling)

(xvi) Procedures according to Section 9, when receiving informed consent from proxy consenters (including matters concerning policies on selection of proxy consenters and explanation and consent according to Sections 8 and 9)

(xvii) Procedures according to Section 9, when receiving informed assent (including matters concerning explanation)

(xviii) If research according to Section 8-8, Method for determining whether or not all of the requirements set forth by said provisions have been met

(xix) If there is any financial burden on or remuneration to human research subjects, etc., an indication and descriptions thereof

(xx) Responses in case of a serious adverse event, if research is invasive

(xxi) If research is invasive, whether or not there is any insurance coverage for compensating health damages caused by the research and descriptions of the compensation

(xxii) Responses concerning provision of medical care to human research subjects after the completion of the research, If research involves medical practices

beyond the extent of ordinary medical examination
(xxiii) Descriptions of operations to be entrusted and method for supervising the entrustee, if a part of the operations relating to the research is to be entrusted
(xxiv) With respect to samples/information being obtained from human research subjects, if there is any possibility of use in a future research that is not yet identified at the time of receiving consent from the human research subjects, etc., or there is any possibility of provision to another research institution for such future research, indication thereof and descriptions of expected contents thereof at the time of receiving the consent
(xxv) Institutional systems and procedures for the conduct, if monitoring and audit of Section 14 are conducted.

1 Section 7(1) sets forth descriptions of a research protocol (excluding the case of (2)). In principle, a research protocol must describe all items from (i) to (xxv) (however, for (xvi) to (xxv), only when applicable). However, depending on the contents, etc. of research, descriptions of some of the items may not always be required. A decision to omit a specific item should be made primarily by the principal investigator, and, the reason for the omission must also be described in the research protocol for review by the ethics review committee and then be approved by the head of the research institution based on "affirmative" opinions of the ethics review committee. In this case, regarding the item to omit, it is desirable to include in the research protocol an indication associated with the records of "affirmative" review in the ethics review committee, and an indication of omission and the reason thereof at the relevant item in the research protocol.
Also, besides matters listed in (1), any matters that are found to be necessary depending on the contents, etc. of the research may be additionally described in the research protocol at the discretion of each research institution.
In addition, necessary documents in connection with the conduct of research (for example, when research uses approved pharmaceuticals or medical devices, a drug package insert of the relevant item, when obtaining informed consent in writing, the written document, etc.) should be arranged to be included in the research protocol, by making associations with the items of the research protocol.

2 In (ii), the "system to carry out the research" includes, when a secretariat is established or when a person charged with security control measures and processing of personal information, etc. of the research is appointed, a system for that purpose, as well. When multi-institutional collaborative research is conducted, it is necessary to clearly describe an indication thereof, names of all research institutions and research cooperative institutions, names of the investigators, name of the person who only provides existing samples/information and name of the institution as affiliation of said person, as well as roles and responsibilities of the representative investigator and the principal investigators in the research institutions (see Section 6-1(4)). In addition, for the person who only provides existing samples/information, it is necessary to describe name of the institution as affiliation of said person if there is any such institution, but, if such person is an individual without affiliation, name of said person suffices. If there are a number of collaborative research institutions and institutions only providing existing samples/information, additional sheets may be used and attach them as an annex of the research protocol.
If institutions only providing existing samples/information need to be added after commencing the research, in principle, it is necessary to amend the research

protocol according to Section 6. However, if it is difficult to identify institutions only providing existing samples/information in advance at the time the research protocol is prepared and a quite large number of such institutions are expected to be involved in the research as providers (for example, registry studies), only under the condition that the research protocol describes as specifically as possible about attributes of those who are expected to be the providers, and the head of the research institution gives approval after receiving opinions of the ethics review committee about the absence of individual identification of all of the providers, it is allowed to take the alternative method of submitting to the ethics review committee a research protocol describing the name of the person who only provides existing samples/information and name of the institution as affiliation of said person, from which samples/information were provided up to the point of submitting a mandated progress report or the like according to Section 11-2(5), together with said mandated report.

3 In (iv), the "method of the research" includes research design, intended number of human research subjects and basis for setting said number (including the case of setting a number of human research subjects without relying on a statistical basis), method for statistical analysis, items to be evaluated and method of evaluation, etc. Also, it includes, when research uses an unapproved pharmaceutical or medical device, a summary of said pharmaceutical or medical device (i.e., so-called "investigator's brochure"), or, when research uses an approved pharmaceutical or medical device, a drug package insert of said pharmaceutical or medical device. If purpose of use includes provision of samples/information to another institution, an indication thereof should be described. For example, when samples/information are to be provided in an institution conducting the collection and provision of samples/information, or when registering data to database, etc. available for use in other kinds of research, indication thereof should be described.
Descriptions of samples/information should include kinds, quantities, etc. suitably for the characteristics of the research. When samples to be used in the research are subjected to genome analysis to obtain genome data which fall in the scope of personal identification code, the research protocol must include such descriptions.
A "period of the research" is from the commencement to the completion of the research, thus, clearly describe the commencement and termination of the research.

4 Regarding (v), as policies for selecting research subjects, when describing a specific method that allows to understand rationality of the selection process and the research subjects have a disease or an abnormality responsive to a drug or the like, special considerations should be given in cooperation with medical doctors on how to notify the name of the disease or an image of conditions corresponding thereto.
If research subjects have a monogenic disease for which there are no established treatments or prophylactic methods and which are associated with mental, intellectual or serious physical disabilities, the principal investigator must review the research particularly carefully on the necessity of the research, any medical or psychological influences to the research subjects and acceptability of research methods giving consideration to these aspects, and the ethics review committee is also required to give particularly careful consideration in reviewing the research.

5 Regarding (vii), if receiving informed consent, also describe matters concerning explanation and consent according to Section 8. If obtaining adequate consent , also describe matters to be explained to obtain adequate consent . If choosing opt-out,

describe the reason thereof and matters to be notified to the human research subject, etc. or to be placed in condition readily available to the human research subjects, etc., regarding the conduct of research as well as the means thereof (such as a sample of documents to be notified to or placed in condition readily available to the human research subjects, etc.). If receiving informed consent in writing, attach to the research protocol for review by the ethics review committee the pertinent documents (the document describing the required information according to Section 8-5 and the consent form), or by electromagnetic means, the explanations by the electromagnetic means and references describing the method of giving consent and descriptions of the explanations (if electronic documents are used as the form describing the required information of Section 8-5 and the consent form, include those forms), or, if choosing opt-out, a sample of documents to be notified to or placed in condition readily available to the human research subjects, etc.

6 Regarding (vii), if there is a plan to receive samples/information from a collaborative research institution or an institution only providing samples/information, the research protocol must include descriptions of how "records regarding the provision of samples/information" set forth in Section 8-3 will be prepared (at what timing, in what storage medium, full name of the investigators who prepare the records, whether or not there are any documents to be prepared separately and be used in place of the records, etc.) and how the records will be stored (where to store, whether or not there are any other institutions which will store the records on behalf of the provider institution as specified in the explanation of Section 8-1(1), etc.) (if there are many occasions of receiving samples/information, the records may be organized as separate sheets). Preferably, the research protocol should also include descriptions of how to confirm what was consented to by the informed consent received by the provider institution when the recipient institution as specified in Section 8-1(1) and (4) receives samples/information.
If matters that are required to be included in the "records regarding the provision of samples/information" are described in the research protocol, a part of the obligations regarding the records will be fulfilled by storing said research protocol itself. In this case, the research protocol is not required to describe all occasions of expected transfer of samples/information one by one with the identification of the provider institution and the recipient institution, as long as the contents of a series of transfer of samples/information are described to the extent that the transfer is traceable at a later date. For details, see the explanation of Section 8-3.

7 Regarding (vii), if there is a plan to provide samples/information to a person in a foreign state (including the case where such provision will be carried out by an entrusted vender), the provision must comply with the procedures specified in Section 8-1(6). Thus, the research protocol must include the descriptions of those procedures (including, if confirmation of establishment of a system conforming to the standards prescribed in Article 16 of the Enforcement Rules for APPI has been made, an indication of such confirmation) and how the records regarding the provision of samples/information will be prepared.

8 In (viii), regarding "handling of personal information, etc.", it is necessary to also describe contents of the measures to be taken for security control of personal information, etc., according to Section 18-1 (of note, the security control measures should have necessary and appropriate contents in accordance with risks originated in the handling practices of personal information, etc. (including the nature and

amount of the personal information, etc., to be handled).
In the case of collaborative research, each of the institutions will determine whether specific information to be used in the research is personal information, etc., but when preparing a research protocol, it is necessary to have a prior discussion with the relevant research institutions, and, during such discussion, arrangement on the handling of personal information, etc., should also be made, as necessary.
Then, the research protocol needs to describe items of personal information, etc. to be used (information such as name, age, sex and history of disease) in the collaborative research, and also describe security control measures in the collaborative research institution and precautions when providing personal information, etc.

9 In (viii), "process(ing)" means deleting all or a part of the descriptions or the like included in personal information, etc. (including replacing with other descriptions, etc.). For example, when deleting descriptions contained in personal information to prepare pseudonymously processed information or anonymously processed information, substituting name contained in personal information with an ID, etc. When processing personal information, etc., it is necessary to also include how and when the processing will be carried out. Likewise, when pseudonymously processed information or anonymously processed information are to be prepared, descriptions must include how and when such processing will be carried out (such as security control measures pursuant to Section 18-1, how to make public, how to respond to complaints and other necessary measures, etc.).

10 In (ix), "risks" are as explained in Section 6-1(2), and also include an adverse event that may be caused in association with the conduct of research (such as an adverse event due to an adverse effect of a drug used in the research in which said drug was administered). Also, in research to be conducted on children as human research subjects, minor invasion to adult such as when performing blood sampling may require descriptions of considerations such as good communication before the invasion and tricks good for distracting during the invasion may also be included.

11 In (x), the "method of storing" must include a description of a period of storage, from the perspective of ensuring traceability of samples/information. In addition, information used in research may be managed by using a cloud service, and, in this case, it is desirable to describe name of the cloud service provider and name of the state where the server storing the information is located. When using a cloud server, see Q&A regarding the "Guidelines on the Act on the Protection of Personal Information".
The "references relating to information to be used in research" include, besides references that support information to be used in research such as data correction history and laboratory notebooks, when samples/information are to be provided to or to be received from another research institution, records regarding the provision of the samples/information.

12 In (xi), the "reporting" is recommended to be in writing, but, since specific contents of a report and method of reporting (including interval of reporting) can vary depending on the contents of research, they should be decided by each research institution.

13 In (xii), as the "source of research funding", describe how the research funding has been obtained such as self-arrangement, donation, based on a contract, etc., and

relationship with the source. If funds or materials are provided by a company related to drugs or medical devices used in the research, describe as such. Examples of situations can be when receiving payment for lecture, manuscript, royalty, etc., besides funds for the research (including scholarship, research grant, etc.), and having stocks (including unlisted stocks and stock options) of such company. Other examples may be issues concerning relationship between the investigators and the company sponsoring the research, such as an employer-employee relationship including consultant or part-time worker, and personal relationship such as kin family. As for how much detail should be described, since there may be variety of cases depending on the research institution and investigator, it should be decided appropriately by the research institution according to the internal rules for the management of conflict of interest (hereinafter, "COI"). Also, research institutions are recommended to prescribe standards for determining whether or not requiring descriptions of situations of COI in a research protocol. If a determination cannot be made easily, it is recommended to seek opinions of the ethics review committee. Regarding COI, it may be helpful to refer to the following documents:

- "Report of Working Group on Conflict of Interest " (November 1, 2002, by Working Group on Conflict of Interest, Academia-Industry Cooperation Promotion Subcommittee, Technology and Research Foundations Section, Council for Science and Technology, MEXT);
- "Guidelines on Management of Conflict of Interest (COI) in Health and Labour Sciences Research" (Ka-Hatsu No. 0331001 of March 31, 2008, Decision by Chief of the Health Science Division).
- "Regarding Management of Conflict of Interest in Clinical Research under the Clinical Research Act" (Iseiken-Hatsu 1130 No. 17 of November 30, 2018, Director of the Research and Development Division, Health Policy Bureau, MHLW)

14 In (xiii), "disclosing information relating to research" includes registration and announcement of Section 6-4 and 6, thus, describe the method thereof.

15 For (xiv), see explanations of Section 10-1 below.

16 In (xv), examples of "systems for allowing human research subjects, etc. and people relevant thereto to make inquiries regarding the research and a point of contact for inquiries" can be clarification of the system for responding to inquiries, etc., establishing an office for receiving inquiries and posting FAQ on the website. For specific responses regarding (xiv) and (xv), see explanations of Section 10 below.

17 In (xvii), "matters concerning explanation" refer to required information to be explained to human research subjects and method of giving explanations.

18 Regarding (xx), when the research is not invasive, it is not always required to describe responses in case of a serious adverse event in a research protocol, however, if a serious adverse event occurs, necessary measures must be provided in accordance with manuals according to Section 15-2(1) and 3. Since the "responses in case of a serious adverse event" of Section 15 include reporting to the head of the research institution, it is necessary to also describe the extent of adverse event to be reported, method of reporting, etc.

19 In (xxi), the "descriptions" are not necessarily limited to those involving payment of money, but include providing medical services, etc. for treating health damages.

20 (xxii) demands the principal investigator to make efforts, such that human research subjects who received research involving medical practices beyond the extent of ordinary medical examination in Section 6-6(4) can receive the best medical services (prophylaxis, diagnosis and treatment) which have been obtained from the results of the research. "After the completion of the research" does not mean when the period of research described in the research protocol has been expired, but means when the medical practice exceeding the extent of ordinary medical examination has been completed on each individual human research subject.

21 In (xxiii), for the "method for supervising the entrustee", see Section 6-1(6) above. Describe in the same manner when a person in a foreign state is used as the entrustee.

22 In (xxiv), examples of "expected contents" can be general descriptions of purpose and contents of research for which the samples/information may be used in the future, purposes of provision to other research institutions and names of research institutions to which the samples/information may be provided.

23 In (xxv), descriptions of the "institutional systems" must include full names of the persons who are engaged in monitoring and/or audit and their relationships with the research institution. Descriptions of the "procedures" must include methods of reporting the results of monitoring and audit.

(2) Matters to be described in a research protocol when conducting the collection and provision of samples/information shall be as given below, unless otherwise specified; provided, however, that this does not apply to matters that have been approved by the head of the research institution upon consideration of opinions of the ethics review committee:

(i) Institutional system to conduct the collection and provision of samples/information (including name of the institution conducting the collection and provision of samples/information and names of the investigators)

(ii) Objectives and significance of conducting the collection and provision of samples/information

(iii) Methods of conducting the collection and provision of samples/information and a period of conducting the same

(iv) Kinds of samples/information subject to the collection and provision

(v) Procedures for obtaining informed consent according to Section 8 (including matters concerning explanation and consent pursuant to said provisions, if informed consent is received)

(vi) Handling of personal information, etc. (including the method of processing if it is to be processed, and the description of preparing pseudonymously processed information and anonymously processed information if such information is to be prepared)

(vii) Burdens on human research subjects and expected risks and benefits, and a comprehensive assessment thereof, and measures for minimizing the burdens and risks

(viii) Methods of storing and quality control of samples/information samples/information

(ix) Handling of samples/information after completion of the collection and provision

(x) Sources of funding regarding the collection and provision of samples/information and any other situations relating to COI of the research institution regarding the collection and provision, and personal incomes and any other situations relating to COI of the investigators regarding the collection and provision

(xi) Responses to inquiries brought by human research subjects, etc. and people relevant thereto

(xii) If there is any financial burden on or remuneration to human research subjects, etc., an indication and descriptions thereof

(xiii) Handling of research results, etc., obtained from the research

(xiv) With respect to samples/information being obtained from human research subjects, if there is any possibility of provision to another research institution for a future research that is not yet identified at the time of receiving consent from the human research subjects, indication thereof and descriptions of expected contents thereof at the time of receiving the consent

1 Section 7(2) sets forth required descriptions in a research protocol for repeatedly and continuously carrying out the collection and provision of samples/information, and operations of so-called banks and archives are the examples thereof. The phrase "when conducting the collection and provision of samples/information" means when collecting and providing samples/information as an "institution conducting the collection and provision of samples/information" set forth in Section 2(14). In principle, a research protocol must describe all items from (i) to (xiv).

However, depending on the contents, etc. of research, descriptions of some of the items may not always be required. A decision to omit a specific item should be made primarily by the principal investigator, and, the reason for the omission must also be described in the research protocol for review by the ethics review committee and then be approved by the head of the research institution based on "affirmative" opinions of the ethics review committee. In this case, regarding the item to omit, it is desirable to include in the research protocol an indication associated with the records of "affirmative" review in the ethics review committee, and an indication of omission and the reason thereof at the relevant item in the research protocol.
Besides matters listed in (2), any matters that are found to be necessary depending on the contents, etc. of the research may be additionally described in the research protocol at the discretion of each research institution.
In addition, necessary documents in connection with the conduct of research should be arranged to be included in the research protocol, by making associations with the items of the research protocol.

2 Regarding (i), see explanations of Section 7(1)(ii) above. In addition, in (i), the "investigators" include persons who are engaged in the collection and provision of samples/information.

3 Regarding (iii), if a period is not specified, an indication thereof must be included.

4 Regarding (v), see explanations of Section 7(1)(vii) above.

5 Regarding (vi), see explanations of Section 7(1)(viii) above.

6 Regarding (vii), see explanations of Section 7(1)(ix) above.

7 Regarding (viii), see explanations of Section 7(1)(x) above.

8 In (ix), "after completion of the collecting and providing" means when the "period" of collecting and providing of samples/information in (iii) has been expired. In addition, even after completion of the collecting and providing, said samples/information must be stored or the like, appropriately according to Section 13.

9 Regarding (x), see explanations of Section 7(1)(xii) above.

10 Regarding (xi), see explanations of Section 7(1)(xv) above.

11 Regarding (xiii), see explanations of Section 7(1)(xiv) above.

12 Regarding (xiv), see explanations of Section 7(1)(xxiv) above.

Chapter 4 Informed Consent, etc.
Section 8 Procedures, etc. for Obtaining Informed Consent

1	Procedures, etc. for obtaining informed consent When the investigators intend to conduct research or a person who is engaged only in providing existing samples/information intends to provide existing samples/information, these persons shall, in principle, obtain prior informed consent on the conduct of the research, as prescribed in the research protocol approved by the head of the research institution and according to the procedures as set forth in (1) to (5) below, or, when providing to those who are in a foreign state, according to the procedures as set forth in (1), (3) or (4) and (6); provided, however, that these do not apply to the case where the provision or receipt of existing samples/information takes place according to the legal or regulatory provisions.

1 Section 8-1 sets forth procedures for obtaining informed consent, etc. "The procedures as set forth in (1) to (5) below" are organized according to the burdens and risks (such as degree of invasion and involvement of intervention) incurred by human research subjects. As to a determination of which procedures should be selected, the determination should be made primarily by the principal investigator in the process of preparing a research protocol, and be reviewed by the ethics review committee including adequacy of the determination.
In addition, (6) below sets forth regarding obtaining "adequate consent " when providing samples/information to a person in a foreign state.
Of note, with regard to the procedures for obtaining informed consent, etc., in addition to (1) to (6) of subsection 1, subsections 2 to 10 need to be complied with, depending on the contents of the research protocol, progress of the research, etc.

2 Note that, in multi-institutional collaborative research, using cloud services or the like to place information in condition for allowing other collaborative research institutions to use or view the information stored in the cloud falls into the definition of "provision" of information to other research institutions.

<Summary of Sections 8-1 to 10 and precautions on the scope of application>

Subsection of Section 8	Precautions on the scope of application
1 Procedures, etc. for obtaining informed consent	- To conduct research, the research protocol need to comply with at least one of (1) to (5) depending on the case. - In addition to (3), (4) applies to persons who are engaged only in providing existing samples/information. - However, these provisions do not apply to the case where the provision or receipt of existing samples/information takes place according to the legal or regulatory provisions. - In addition to any of (1) to (5) applicable to the case, (6) applies when providing a person in a foreign state with samples/information to be used in the research (including the case where all or part of the handling of the samples/information is entrusted to a vender).
2 Obtaining informed consent by electromagnetic means	- This applies when obtaining informed consent by electromagnetic means in place of writing.
3 Records regarding the provision of samples/information	- This applies when a research institution receives samples/information from a collaborative research institution or a person who is only engaged in the provision of samples/information.
4 Amendment of a research protocol	- This applies to the case where the research protocol is amended to conduct research.
5 Matters required to be explained	- In the procedures of subsection 1, this applies when informed consent is obtained.
6 Matters that should be notified to human research subjects, etc., or be placed in a condition readily available to human research subjects, etc.	- In the procedures of subsection 1, this applies when information of research is notified to the human research subjects, etc., or is placed in a condition readily available to human research subjects, etc.
7 Procedures for using samples/information in research which was not specified at the time of obtaining consent	- This applies to the case where explanation of the purpose, etc. of using samples/information which are expected at the time of obtaining consent from human research subjects, etc. has been given to the extent that is possible, and then a new purpose, etc. of use is subsequently identified.
8 Handling of research in a situation where there is an immediate and clear danger to the life of the human research subject	- This applies when research is to be conducted in a situation where there is an immediate and clear danger to the life of the human research subject.
9 Simplifying the procedures of informed consent	- This applies when research in which the procedures of subsection 1 or 4 can be simplified is to be conducted.
10 Withdrawal, etc. of consent	- This applies when the human research subjects, etc. have withdrawn or refused the consent.

3 It is important to note that the scope of application of the phrase "when a person who provides existing samples/information intends to provide existing samples/information" encompasses, besides the investigators (see Section 2(17)), other persons than the investigators (i.e., persons who are engaged only in providing existing samples/information in an organization other than research institutions).
In other words, Sections 4 and 5, etc. do not apply to people other than the investigators (i.e., persons who are engaged only in providing existing samples/information) and the head of the institution being the employer of these people, but Section 8-1(3), (4) and (6) and 8-3 apply to these people.

4 The phrase "these persons shall, in principle, obtain prior informed consent" means that some of "the procedures as set forth in (1) to (5) below" are stipulated as being "not necessarily required to obtain informed consent". In addition, when research is conducted in a phased manner in accordance with the progress of the research, contents of the research to be performed in the future must also be described in the research protocol and explained to the human research subjects, etc. in advance.

5 The "case where the provision of existing samples/information according to the legal provisions" intends, for example, providing information registered in the National Cancer Database or the Prefectural Cancer Database in accordance with the provisions of the Cancer Registration Promotion Act and providing questionnaire information, etc. of statistical surveys in accordance with the Statistics Act.

6 The "case where the receipt of existing samples/information takes place according to the legal or regulatory provisions" includes, for example, the case of receiving information registered to the National Cancer Database and the Prefectural Cancer Database based on the Cancer Registration Promotion Act as existing samples/information, and the case of receiving questionnaire information, etc. of statistical surveys based on the provisions of Statistics Act.
Also, when receiving data according to the provisions of the Guidelines (MHLW Public Notice No. 424 of 2010) for the use or provision of information provided to the Minister of Health, Labour and Welfare by insurers and prefectural associations of medical care services for older senior citizens based on Article 16(2) of the Act on Assurance of Medical Care for Elderly People (Act No. 80 of 1982), as well, this can be deemed to be the "case where the receipt of existing samples/information takes place according to the legal or regulatory provisions".

7 When genome data are to be newly acquired by conducting genome analysis, etc. of samples, information including said genome data for use in the research may fall into the scope of personal information or special care-required personal information. Therefore, fully describe in a research protocol the contents of the genome analysis, including indication of whether or not the genome analysis will be conducted on samples, and perform the procedures for obtaining informed consent, etc. prescribed in subsection 1(1) to (6).
When genome data falling into the scope of personal identification code are to be acquired by conducting genome analysis, etc. of samples, an indication thereof must be included in the research protocol (including descriptions for obtaining consent). In addition, when genome analysis which were not originally planed before starting the research are to be conducted, it is necessary to complete the procedure of

amendment of the research protocol, and, where applicable, the procedures of informed consent, etc. may need to be revised.

8 There are additional regulations on acquisition, use and provision in administrative organs, so, other than these Guidelines, see Chapter 5 of APPI, the Guidelines on Acts on the Protection of Personal Information (Administrative Organs), the Guidebook on Clerical Responses to Acts on the Protection of Personal Information (For Administrative Organs) and Q&A regarding the Acts on the Protection of Personal Information (Administrative Organs), etc. For regulations on acquisition, use and provision in organs of local governments and regional independent administrative corporations, see the provisions of the relevant local government, etc., in addition to these Guidelines.

(1) When samples/information are newly acquired to conduct research:
The investigators shall conduct the procedures A or B below.
Of note, the investigators need to conduct the procedures A or B by themselves even in the case where they newly acquire samples/information for the research via a research cooperative institution. In addition, the research cooperative institution must confirm that the procedures have been completed:

A Invasive research:
The investigators shall obtain informed consent in writing, using a written document containing the matters required to be explained according to subsection 5 below.

B Non-invasive research:

(a) Research involving intervention
The investigators are not necessarily required to obtain informed consent in writing, but, when they receive informed consent other than in writing, they shall obtain informed consent verbally on the matters required to be explained according to subsection 5 below, and prepare records as to how and what explanation was given and what was consented to.

(b) Research not involving intervention

I) Research using samples
The investigators are not necessarily required to obtain informed consent in writing, but, when they receive informed consent other than in writing, they shall obtain informed consent verbally on the matters required to be explained according to subsection 5 below, and prepare records as to how and what explanation was given and what was consented to.

II) Research not using samples

(i) When acquiring special care-required personal information:
The investigators are not necessarily required to obtain informed consent, but, if they do not obtain informed consent, in principle, they need to obtain adequate consent of human research subjects, etc. However, in the case where an opportunity is guaranteed for the human research subjects, etc. to express refusal against the conduct or continuation of the research are ensured, if the requirements of 9(1)(i) to (iii) are met and either one of the following requirements is met, special care-required personal information may be acquired and used, provided that appropriate measures from among those listed in Section 9(2)(i) to (iii) are taken:

a In the case where it is necessary for a research institution which falls into academic research institutions to acquire the special care-required personal information for academic study purposes, when there is no likelihood that rights and benefits of the human research subjects are unjustly infringed; and

b In the case where there are special circumstances for the research institution to acquire the special care-required personal information to conduct research, when there is a difficulty in obtaining informed consent from the human research subjects, etc.

(ii) Other than (i) above:
The investigators are not necessarily required to obtain informed consent, but, when they do not obtain informed consent, they shall notify to the human research subjects, etc., the matters of subsection 6(i) to (ix), or place said matters in a condition readily available to human research subjects, etc., and guarantee an opportunity for the human

research subjects, etc. to express their refusal of the conduct or continuation of the research (however, when information (excluding special care-required personal information) to be used in research is to be provided to a collaborative research institution, the provision of (3)B apply *mutatis mutandis*).

1 Section 8-1 (1) sets forth procedures of informed consent when samples/information are newly acquired to conduct research. In subsection 1(1), the phrase "when samples/information are newly acquired to conduct research" means when samples/information are acquired from the human research subjects during the conduct of the research in order to be used in the pertinent research. Examples of a method for acquiring samples/information from human research subjects can be blood sampling, health examination, questionnaire survey, etc. which are conducted for the research.
However, as pointed out in the explanations of Section 2, "(7) existing samples/information", samples/information acquired from human research subjects for a purpose other than the pertinent research fall under the category of "existing samples/information". Therefore, when such existing samples/information are provided to the research as a secondary use, this is not the case of "when samples/information are newly acquired to conduct research". For example, when using medical records which describe information acquired from human research subjects for medical services not for research purposes for secondary use in the research does not fall into the case of acquiring from human research subjects for the pertinent research. Therefore, this is not the case of "when samples/information are newly acquired to conduct research". On the other hand, when the purpose of using the samples/information already exists at the time of acquiring them from the human research subjects, it falls into the case of "when samples/information are newly acquired to conduct research", even if the samples/information are acquired from the human research subjects for the purpose of medical service, at the same time.
When samples/information are newly acquired from human research subjects to conduct multi-institutional collaborative research, informed consent obtained from the human research subjects, etc. at any one of the collaborative research institutions based on the provision of subsection 1(1) will suffice.

2 "The case where they newly acquire samples/information for the research via a research cooperative institution" is limited to the case which does not involve invasion or involves minor invasion such as blood sampling or the case where information to be used in research is to be acquired. The investigators should note that, not only when acquiring samples/information directly from the human research subjects, but also when acquiring samples/information indirectly through a research cooperative institution, the investigators themselves need to conduct the procedures of obtaining informed consent.

(Reference) Regarding provision of personal data to the investigators of a research cooperative institution (Relationship with APPI)

Under APPI, when a research cooperative institution provides personal data to the investigators, in principle, it needs to obtain consent of the person him/herself (APPI, Article 27(1)). In this regard, in these Guidelines, the investigators, when newly acquiring samples/information through the research cooperative institution, obtain the consent in place of the research cooperative institution in the "procedures of obtaining informed consent.

Of note, under APPI, it is acceptable that the research cooperative institution provides personal data to the investigators, in association with the entrustment (APPI, Article 27(5)(i)). It should be noted, however, that, in this case, the research cooperative institution to be the entrustee is only able to handle the personal data within the extent of the operation entrusted by the investigators, and thus is not allowed to handle the personal data in other operations.

The investigators must show to the research cooperative institution that they are taking the procedures of Section 8-1(1)A or B, before theresearch cooperative institution acquires samples/information from the human research subjects.
It should be noted that Section 8-3(1) applies to the research cooperative institution, as well, for the provision of samples/information to the research institution.

3 "Obtaining informed consent in writing" is when explanation is given in writing and consent is given in writing. "Obtaining informed consent verbally" is when explanation is given verbally and consent is given verbally. In addition, when either one of explanation or consent is given in writing and the other verbally, the case is treated that "obtained informed consent verbally".

4 The explanation in writing or verbally when obtaining informed consent may not necessarily be given individually or in person.
When the explanation is given in writing, it may also be given by handing out a written document to a group of people or giving explanation to the group, or by sending by post a document for explanation which has been prepared in such a manner that the reader can easily understand the contents. However, the human subject's expression of giving consent must be confirmed in writing individually on each of the human research subjects, including the case where the human subject responded by post. In addition, it is necessary to provide an opportunity for research subjects, etc. to make questions on the contents of the explanation by establishing a point of contact or presenting contact information such as phone number, etc. Simply putting up a sheet describing the explanation on a bulletin board in a venue of meeting place is not recognized to be giving explanation in writing.
When obtaining informed consent from human research subjects, etc. who are unable to read documents for explanation and consent or when obtaining informed consent from human research subjects, etc. who are unable to sign a consent form due to paralysis, etc., it is recommended to give special considerations such as allowing a witness to be present and sign the consent form on behalf of the human research subjects. However, such a "witness" must be a person who does not engage in the conduct of the relevant research, in order to eliminate undue influences from the investigators.
When explanation is given verbally, it may also be given by holding a briefing meeting and by phone. However, the will of giving consent must be confirmed in writing individually on each of the human research subjects, including the case where a response is made by phone or by post.

5 In B(a), required contents of the "records as to what was consented to" are date of consent, method of explanation, person who gave explanation, matters being consented, etc. When the descriptions of the matters include matters relating to the provision of samples/information to another collaborative research institution, said "records as to what was consented to" may be stored as the "records regarding the

provision of samples/information" set forth in Section 8-3.
Also, even if the procedures are performed verbally, it is desirable to give such consideration as providing references for the contents of explanation and consent (especially when the research subjects, etc. request to do so), so that the human research subjects, etc. can remember the contents of explanation being given and consent that they gave.

6 The scope of research falling into the scope of B(b)(II) is intended to cover those that involve neither invasion nor intervention, and information to be used in research is collected by means of a questionnaire, interview, observation, etc. Ob note, procedures, etc., for informed consent are different according to whether or not information to be collected includes "special care-required personal information". For the definition of "special care-required personal information", see the explanation of Section 2(29), "special care-required personal information".

7 When adequate consent has been obtained, preparation of records as to what was consented to is not required, but when adequate consent is obtained to provide the acquired samples/information to a collaborative research institution, preparing and storing of records regarding the provision of samples/information will be required as set forth in Section 8-3 above. Thus, when obtaining adequate consent, the institutions should consider preparing and storing records as to what was consented to for each individual human research subject, etc., including the recording matters required as records regarding the provision of samples/information.

8 In B(b)(II)(i), in principle, since APPI requires to obtain consent of the person him/herself when acquiring special care-required personal information, it is necessary to fulfill the requirements prescribed in the items of Article 20(2) of APPI in order to simplify the procedures based on the provisions of Section 8-9 (in this case, B(b)(II)(i)a or b) (for details of the provisions of Section 8-9, see the explanations of Section 8-9).

9 In B(b)(II)(i)a, the term "academic studies" means discovery of a new law or principle, establishment of analysis or methodology, systematization of new knowledge or application method thereof, opening up a new horizon of the state-of-the-art discipline. Of note, when handling personal information for the purpose of product development, the activity is not considered to be for academic study purposes.
It also requires appropriate operations such as providing measures for not to unlawfully infringe someone's individual rights and benefits. In this regard, even if an academic research institution uses personal information for a different purpose, out of the need for academic study purposes, it is desirable to take possible measures in view of the purpose of the academic studies, such as processing personal information so that a specific individual cannot be identified, from the perspective of protecting the person's or third party's rights and benefits.
"The case where it is necessary to obtain the special care-required personal information for academic study purposes" includes when a part of the purpose of obtaining the special care-required personal information is for academic study purposes.

10 In B(b)(II)(i)b, "the case where there are special circumstances, when there is a difficulty in obtaining informed consent from the human research subjects, etc."

means the cases which are prescribed in Article 20(2)(ii), (iii) and (iv) of APPI. For interpretation of Article 20(2)(ii), (iii) and (iv) of APPI, see the APPI Guidelines (Common Provisions) and the Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information".
"When there is a difficulty in obtaining informed consent from the human research subjects, etc." is, for example, research for which the procedures can be simplified can be when there is a potential of creating bias in the results of research by informing the purpose of the survey in advance. This provision is intended to apply only to the case where there is a difficulty in conducting the research or the value of the research will be undermined considerably, if the procedures are not simplified. Whether or not a case falls under either a or b is primarily determined by the principal investigator according to APPI, and it is necessary to present the reason thereof to the ethics review committee for review, and then obtain approval of the head of the research institution.

11 In B(b)(II)(i), regarding "guarantee an opportunity for the human research subjects, etc. to express their refusal of the conduct or continuation of the research", when human research subjects, etc. have refused to be a subject to the conduct of research, the individual human research subject relevant to the refusal cannot be chosen to be a subject to the research, and responses to such human research subject need to be made according to Section 8-10. In this case, personal information of the refused human research subjects, etc. will not be collected, but, it is possible to add to the population of the research subjects when aggregating the results of the research to use basic demographic characteristics of the person (such as sex and age), etc.

12 In B(b)(II)(ii), regarding "the matters of subsection 6(i) to (ix)", when research is to be conducted by using newly acquired samples/information, it is possible to adopt the method which includes notifying the matters of Section 8-6(i), (ii) and (vi) to (ix) to the human research subjects, etc., or placing the same in a condition readily available to the human research subjects, etc., and then guaranteeing an opportunity for the human research subjects, etc., to refuse the conduct or continuation of the research (i.e., opt-out). For "notifying" and "placing in a readily available condition", see explanations of Section 8-6.

(2) When using existing samples/information available at the investigators' research institution in research:
The investigators shall follow the procedures A or B below:

A Research using samples
The investigators are not necessarily required to obtain informed consent in writing, but, when they receive informed consent other than in writing, they shall obtain informed consent orally on the matters required to be explained according to subsection 3 below, and prepare records as to how and what explanation was given and what was consented to. However, when there is a situation falling under any of the following categories, said procedures may not be required:

(a) When all of the existing samples/information fall under any of the following categories:
(I) when the existing samples are already in a condition that a specific individual cannot be identified, use of the existing samples does not enable to obtain personal information;
(II) information to be used in the research is pseudonymously processed information (limited to those that has already been available);
(III) when there is a difficulty in obtaining informed consent, information to be used in the research is anonymously processed information; and
(IV) information to be used in the research is individual-related information.

(b) In the case where (a) is not applicable, when there is a difficulty of obtaining informed consent and the human research subjects, etc., gave consent only on other research in absence of explicit indication of use in the pertinent research at the time that the existing samples/information were obtained, all of the following requirements are met:
(I) Regarding the conduct of said research, the matters of subsection 6(i), (ii), (vi) and (vii) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.; and
(II) It is reasonably found that there is a reasonable relationship between the consent and the purpose of said research.

(c) In the case where neither (a) nor (b) is applicable, when the existing samples/information are used in socially highly important research, and when the matters of subsection 6(i), (ii) and (vi) to (ix) have been notified to the human research subjects, etc., and then adequate consent was obtained, or when all of the following requirements (I) to (III) are met:
(I) Any of the following requirements is met:
(i) when a research institution being an academic research institution needs to handle the existing samples/information for academic study purposes, there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects; and
(ii) when there is a special circumstance in conducting the research, and there is a difficulty in obtaining informed consent and adequate consent from the human research subjects, etc.
(II) Regarding the conduct of said research, the matters of subsection 6(i), (ii), and (vi) to (ix) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.; and
(III) In principle, the human research subjects, etc., are guaranteed with an opportunity to refuse to have conducted or continued with the research.

B Research not using samples
The investigators are not necessarily required to obtain informed consent. However, when they do not obtain informed consent, any of the following must be met:

(a) Information to be used in the research is pseudonymously processed information (limited to those that has already been available), anonymously processed information or individual-related information:

(b) In the case where (a) is not applicable, when the human research subjects, etc., gave consent only on other research in absence of explicit indication of use in the pertinent research at the time that the information to be used in said research were obtained, all of the following requirements are met:

(I) Regarding the conduct of said research, the matters of subsection 6(i), (ii), (vi) and (vii) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.; and

(II) It is reasonably found that there is a reasonable relationship between the consent and the purpose of said research.

(c) In the case where neither (a) nor (b) is not applicable, when the matters of subsection 6(i), (ii) and (vi) to (ix) have been notified to the human research subjects, etc., and then adequate consent was obtained, or when all of the following requirements (I) to (III) are met:

(I) Any of the following requirements is met:

(i) when a research institution being an academic research institution needs to handle the information to be used in the research for academic study purposes, there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects; and

(ii) when there is a special circumstance in conducting the research, and there is a difficulty in obtaining adequate consent from the human research subjects, etc.

(II) Regarding the conduct of said research, the matters of subsection 6(i), (ii) and (vi) to (ix) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.; and

(III) In principle, the human research subjects, etc., are guaranteed with an opportunity to refuse to have conducted or continued with the research.

1 Section 8-1(2) set forth procedures of informed consent when conducting research using existing samples/information available at the investigators' research institution. Research falling under the provision of A, i.e., when using samples, is required to perform the procedures of informed consent in writing (which may be replaced with electromagnetic means) or verbally, in principle. However, only if there is a situation that falls under any one of A(a) to (c), the existing samples/information available at the research institution can be used without performing said procedures. For research falling under the provision of B, i.e., when not using samples, may not be necessarily required to obtain informed consent, and opt-out, etc. may be chosen.

2 In (2), examples of the "available at the investigators' research institution" include when a research institution possesses samples/information acquired at the time of conducting another research that took place in the past, and when a corporation or the like that owns a medical institution possesses samples/information acquired at the medical institution through a medical examination not for research purposes.

3 In A(a)(I), "when the existing samples are already in a condition that a specific individual cannot be identified" refers to a condition in which samples do not allow identification of a specific individual even if collated with other information, etc., before the commencement of the research.
If a specific individual can be identified by collating information described in a label or the like affixed to the samples with medical records or so-called "matrix table", etc., this is not the case of "a specific individual cannot be identified". Further, for example, in the case where the section that conducts the research does not keep the matrix table, when another section in the same corporation keeps the matrix table and a specific individual can be identified by collating with the matrix table by using a common method in the ordinary operation, this is not the case of "a condition that a specific individual cannot be identified". For the understanding of the matrix table, see explanations of Section 2(34).

4 In A(a)(I), "use of the existing samples does not enable to obtain personal information" is when personal information would not be obtained by analyzing or the like of samples in the conduct of the research. If it is expected to obtain genome data falling into the scope of personal identification code by conducting genome analysis, even if the samples prior to the genome analysis are in a condition that unable to identify a specific individual, this is not the case.

5 When using samples derived from a dead person (such as excavated bones) from which no blood relatives who are currently alive cannot be speculated, this is the case of A(a)(I).

6 In A(a)(II), regarding "... is pseudonymously processed information (limited to those that has already been available)", this is when using pseudonymously processed information which had already been created prior to the drafting of the pertinent research protocol in the research. It does not include the case where existing samples/information are analyzed and processed for the purpose of conducting the research to newly create pseudonymously processed information. Of note, under APPI, when the purpose of using pseudonymously processed information being personal information has been amended, the amended purpose of use must be made open to public, in principle.

7 In A(a)(III), for "when there is a difficulty in obtaining informed consent", see point 12, the explanation of "when there is a special circumstance in conducting the research, and there is a difficulty in obtaining informed consent and adequate consent from the human research subjects, etc." below.

8 In A(a)(III), "... is anonymously processed information" includes when existing samples/information are analyzed and processed to newly create anonymously processed information and when using already created anonymously processed information in research. It should be noted that, under APPI, when anonymously processed information has been created, items of information relating to an individual contained in the anonymously processed information need to be made public promptly after the creation of the anonymously processed information.
Of note, as prescribed in Section 3-1C(iii), research in which only already available anonymously processed information is used is out of the scope of application of these Guidelines. For example, when using already available anonymously

processed information in research with other samples/information is not applicable to these Guidelines.

9 In A(b), "at the time that the existing samples/information were obtained, consent of the human research subjects, etc. was given only on different research in absence of explicit indication of the pertinent research" refers to a case where the samples are to be used for a purpose that is different from the one that was explicitly identified in the earlier research for which consent was given.

10 In A(b)(II), "it is reasonably found that there is a reasonable relationship between the consent and the purpose of said research" means when the head of the research institution has given approval based on the results of review by the ethics review committee on the fact that there is a relationship between the earlier research and the research to be conducted, such as when additional research is to be conducted for a same purpose as that of the earlier research.

11 In A(c), an example of "socially highly important research" refers to research relating to prophylaxis or treatment of an important disease in terms of public health, which is in need of making use of samples/information (including those that can be readily collated with other information and thereby identify a specific individual) which enables identification of specific individuals, based on a systematic cooperation of the whole society.
When the research is to be conducted using samples based on this provision, the ethics review committee should determine the adequacy of the research from the perspective of weighing up the protection of human research subjects against the outcome obtainable from the research, using references such as the "Policies on the research and development involving the use of human tissues removed by surgery, etc." (report of the Health Sciences Council of December 16, 1998).

12 In A(c)(I)(ii), "when there is a special circumstance, and there is a difficulty in obtaining informed consent and adequate consent from the human research subjects, etc." is the cases which are specified in APPI, Article 18(3)(ii) to (iv). Interpretation of "the case where there is a special need to enhance public health or promote healthy development of children, when it is difficult to obtain consent of the person him/herself" (APPI, Article 18(3)(iii)) is explained in the Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information" as follows:

Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information" (exceptions of limitation by purpose of use)

Q: A medical institution intends to use a clinical case of its former patient, for an observational study which is not included in the scope of the purpose of use, in the premises of the medical institution. When effective contact information is not kept due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the research in view of the time and costs for obtaining consent, is it possible to use it in absence of consent of said patient?

A: A personal information handling business operator cannot handle personal information in absence of advance consent of the person him/herself, exceeding the extent that is necessary to achieve a specified purpose of use; however, when there is a particular necessity in order to enhance public health, and there is a difficulty in obtaining the person's consent, the

business operator is allowed to handle the personal information in absence of advance consent of the person, exceeding the extent that is necessary to achieve the original purpose of use (APPI, Article 18(3)(iii)).
In general, utilizing clinical cases of a medical institution for an observational study in the medical institution or for enhancing medical techniques such as diagnosis and treatment can be considered to especially contribute to enhance public health, because the results of the research are to be widely shared and utilized, or it makes it possible to provide better medical service to unspecified many patients who receive medical services at the medical institution.
In addition, when medical institutions do not have effective contact information due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the study by obtaining consent from said former patient in view of the time and costs for obtaining consent, it is considered to fall under the case "when it is difficult to obtain consent of the person him/herself".
Therefore, in the case where a medical institution uses personal information of its patient's clinical case kept by said medical institution for the purpose of an observational study, when the medical institution does not have effective contact information due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the study by obtaining consent from said former patient in view of the time and costs for obtaining consent, it is considered that the medical institution is allowed to do so according to said provision.
Of note, however, in principle, the medical institution is not able to handle the data exceeding the extent that is necessary to achieve the original purpose of use and the new purpose, i.e., use in said study.
Besides, it should be noted that medical institutions are required to comply with the guidelines on medical research, etc., which stipulate involvement of the ethics review committee, ensuring opportunities for human research subjects to refuse, publication of research results, etc., and relevant legal and regulatory provisions.
(Added in May 2022)

For interpretation of Article 18(3)(ii) to (iv) of APPI, see the APPI Guidelines (Common Provisions) and the Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information".

13 In A(c)(II), regarding "notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc." and, in (III), "an opportunity for the human research subjects, etc. to express refusal is ensured", see the explanation of Section 8-1(1)B(b)(II)(ii)(opt-out).
In addition, in (III), the reason why it is "in principle" is that there may be a case where, for example, the handling of samples/information is refused by the human research subjects, etc., but there is a difficulty in identifying the samples/information of said human research subjects, etc., to eliminate them from the scope of research (e.g., when only genome data are kept).

14 In A(c)(I) and B(c)(I), for "academic study purposes", see explanations of Section 8-1(1)B(b)(II)(i)a.
Regarding "when ... needs to handle the existing samples/information for academic

study purposes", it includes the case where a part of the purposes of handling special care-required personal information is for academic study purposes.

15 In B(c)(II)(ii), for "special circumstances", see the explanations of point 12 above.

16 In B(c)(III), for "in principle" and "an opportunity for the human research subjects, etc. to express refusal is ensured", see the explanations of point 13 above.

(3) When providing existing samples/information to another research institution:
Persons who are engaged in the provision of existing samples/information shall follow the procedures of A and B below:

A When providing existing samples and special care-required personal information
Informed consent is not necessarily obtained in a written form, but if informed consent is not obtained in writing, consent on the matters to be explained listed in subsection 5 (including consent on the provision of the existing samples and special care-required personal information) must be obtained verbally, and a record on the method and contents of explanation and the contents of the consent. However, in the case where there is a difficulty in fulfilling these procedures, when either of the following requirements is met, it is not required to fulfill said procedures:

(a) when providing only existing samples which are in a condition not to be able to identify a specific individual, personal information will not be acquired in the recipient research institution of the existing samples by using the existing samples; and

(b) in the case where (a) is not applicable, when all possible efforts have been made to provide an opportunity for the human research subjects, etc., to refuse the provision of the existing samples and special care-required personal information, and when any of the following requirements is met, all requirements listed in subsection 9(1) are met and appropriate measures according to subsection 9(2) are taken,

(i) when it is necessary for a research institution being an academic research institution to provide the existing samples and special care-required personal information to a collaborative research institution for academic study purposes, there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects

(ii) when a research institution being an academic research institution intends to provide the existing samples and special care-required personal information, it is necessary for the research institution to do the handling for academic study purposes, and there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects

(iii) when there is a special circumstance in providing the existing samples and special care-required personal information, there is a difficulty in obtaining adequate consent from the human research subjects, etc.

(c) In the case where neither (a) nor (b) is applicable, when the matters of subsection 6(i) to (v), (viii) and (ix) have been notified to the human research subjects, etc., and then adequate consent has been obtained, or when all of the following requirements (i) to (iii) are met:

(i) Any of the requirements (b)(i) to (iii) are met;

(ii) Regarding the conduct of said research and the provision of the existing samples and special care-required personal information to another research institution, the matters of subsection 6(i) to (v), (viii) and (ix) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.; and

(iii) Regarding the provision of the existing samples and special care-required personal information, in principle, the human research subjects, etc., are guaranteed with an opportunity to refuse.

B Cases other than A:
When providing research information (excluding special care-required personal

information) to be used in research, informed consent is not necessarily required to obtain, but when informed consent is not obtained, in principle, adequate consent must be obtained; however, said procedures are not required when any of the following (a) to (c) are met:

(a) When information to be used in the research is individual-related information, either of the following is met:
  (i) when the research institution to be the recipient is not expected to acquire the individual-related information as personal information; and
  (ii) in the case where the research institution to be the recipient is expected to acquire the individual-related information as personal information, when any of A(b)(i) to (iii) becomes applicable by replacing the phrase "samples and special care-required personal information" in the provision of A(b)(i) to (iii) with "individual-related information", or when the person who performs the provision of information to be used in the research has confirmed that adequate consent of the human research subjects, etc. was obtained in the research institution to be the recipient,

(b) In the case where (a) is not applicable, when there is a difficulty of obtaining adequate consent, when either of the following is met:
  (i) when information to be used in the research is anonymously processed information; and
  (ii) in the case where (i) is not applicable, when all possible efforts have been made to provide an opportunity for the human research subjects, etc., to refuse the provision of the information to be used in the research, when any of A(b)(i) to (iii) becomes applicable by replacing the phrase "samples and special care-required personal information" in the provision of A(b)(i) to (iii) with "information to be used in the research", all requirements listed in subsection 9(1) are met and appropriate measures according to subsection 9(2) are taken,

(c) In the case where information to be used in the research is applicable to neither (a) nor (b) and there is a difficulty in obtaining adequate consent, when, in A(c) above, the phrase "in the case where neither (a) nor (b) is applicable, when the matters of subsection 6(i) to (v), (viii) and (ix) have been notified to the human research subjects, etc., and then adequate consent has been obtained, or" is deleted and the phrase "samples and special care-required personal information" is replaced with "information to be used in the research", the requirement of A(c) is met.

1 Section 8-1(3) sets forth procedures of informed consent, etc. when providing existing samples/information to another research institution. When the case is applicable to A (when providing existing samples and special care-required personal information), in principle, it is required to perform procedures of informed consent in writing or verbally. When the case is applicable to B (when providing information to be used in research which is other than special care-required personal information), if not obtaining informed consent, in principle, adequate consent should be obtained. As for (3), "existing samples/information", see explanations of Section 2(7).

2 The investigators need to perform the procedures of Section 8-1(3) when providing existing samples/information to other research institutions, but when the provision takes place associated with (i) entrustment (see APPI, Article 27(5)(i)), or (ii) joint use (see APPI, Article 27(5)(iii)), it is not necessary to perform the procedures of Section 8-1(3). However, of note, when the provision takes place associated with (i) entrustment, the institution of the recipient needs to handle the samples/information

within the extent of the entrusted operation, or when the provision takes place associated with (ii) joint use, the research institution being the recipient needs to handle the samples/information only within the extent of the specified purpose of use thereof.
In the case of multi-institutional collaborative research, it is considered that the investigators' provision to a third party is basically based on Article 27(1) of APPI, but they are not kept from providing samples/information associated with (ii) joint use.

3 As for pseudonymously processed information, since it is presumed to be used internally in a research institution, third party provision is, in principle, prohibited under APPI. Thus, Section 8-1(3) does not stipulate third party provision (provision to anther research institution) of pseudonymously processed information. However, under APPI, provision of pseudonymously processed information is possible when it is associated with entrustment or joint use (see APPI, the items of Article 27(5) that apply mutatis mutandis with necessary replacement by Article 41(6), and the items of Article 27(5) that apply mutatis mutandis with necessary replacement by Article 42(2)), in these Guidelines, as well, the investigators may provide pseudonymously processed information to another research institution associated with entrustment or joint use.

4 In (3)A, for "the case where there is a difficulty in fulfilling these procedures", see explanations of "when there is a difficulty in obtaining informed consent" in Section 8-1(2)A(a)(III).

5 Regarding (3)A(a), B(a)(i), (ii) first part, and (b)(i), the procedures, etc., of informed consent are not required to the following:
(i) A(a): Samples in a condition not to be able to identify a specific individual (when use of the existing samples does not enable to obtain personal information, and there is a difficulty in performing the informed consent procedures);
(ii) B(a)(i): Individual-related information (when the research institution to be the recipient is not presumed to acquire the individual-related information as personal information);
(iii) B(a)(ii)first part: Individual-related information (when the research institution to be the recipient is presumed to acquire the individual-related information as personal information, and applicable to the exceptions prescribed in the items of Article 27(1) of APPI); and
(iv) B(b)(i): Anonymously processed information (when there is a difficulty in obtaining adequate consent).
For "a condition not to be able to identify a specific individual" and "use of the existing samples does not enable to obtain personal information", see explanations of Section 8-1(2). For "presumed to acquire the individual-related information as personal information", see the explanations below.
Of note, under APPI, prior to third party provision of anonymously processed information, items of information relating to an individual contained in the anonymously processed information to be provided to a third party and the method of the provision must be made public, and it is required to clearly indicate to the third party that the information to be provided is anonymously processed information.

6 Regarding (3)B(a), the following cases are allowed to do third party provision of individual-related information:

(i) B(a)(i): when the research institution to be the recipient is not presumed to acquire the individual-related information as personal information;
(ii) B(a)(ii): when the research institution to be the recipient is presumed to acquire the individual-related information as personal information, and applicable to either of the following conditions:
- when applicable to the exceptions prescribed in the items of Article 27(1) of APPI; and
- the research institution to be the provider has confirmed that adequate consent of the human research subjects, etc. was obtained in the research institution to be the recipient,

In B(a)(ii), regarding "adequate consent of the human research subjects, etc. was obtained in the research institution to be the recipient", the subject that obtains adequate consent is the research institution to be the recipient, but it is also permissible that the research institution to be the provider obtains adequate consent on their behalf, on the premise that the same level of protection of rights and benefits of the human research subject are ensured.
Of note, when B(a)(ii) is applicable, in the research institution to be the recipient, it is necessary to follow the procedures according to Section 8-1(2)B to conduct the research (Section 8-1(5)B(a)).

7 In (3)B(a)(i) and (ii), to "acquire the individual-related information as personal information" means when individual-related information is added or the like to personal information in the research institution to be the recipient, so that it can be used as personal information. When the research institution to be the recipient adds the provided individual-related information to other personal information that the recipient has via an ID, this is the case that "acquires as personal information".
In addition, the word "presumed" means when the research institution to be the provider actually presumes that the research institution to be the recipient "acquires as personal information", or when it can be generally presumed that it "acquires as personal information" from the perspective of the general person (perspective based on the ability of judgement and understanding of research institutions which undertake the same kind of research). Of note, when an agreement or the like between the research institution to be the provider and the research institution to be the recipient specifies that the research institution to be the recipient does not use any provided individual-related information as personal information, it is generally not presumed to "acquire as personal information".

8 Regarding (3)A(b) and B(b)(ii), when all of the following requirements are met, the procedures, etc., of informed consent can be simplified:
(i) there is a difficulty in obtaining informed consent (when providing existing samples and special care-required personal information) or adequate consent (when providing information to be used in research other than special care-required personal information);
(ii) it is applicable to exceptions prescribed in the items of Article 27(1) of APPI); and
(iii) all of the requirements listed in Section 8-9(1) are met.

When informed consent procedures are to be simplified, it is not necessarily required to guarantee an opportunity to refuse for the human research subjects, etc., and making all efforts to provide the human research subjects, etc., with an opportunity to refuse.
In addition, under APPI, since it is, in principle, necessary to obtain consent of the

person him/herself for third party provision, in order to simplify the procedures based on the provisions of Section 8-9, it is necessary to meet the requirements for exceptions prescribed in the items of Article 27(1) of APPI (i.e., (ii) above) (for details of the provisions of Section 8-9, see explanations of Section 8-9).

(3) In A(b)(iii), "when there is a special circumstance, and there is a difficulty in obtaining adequate consent from the human research subjects, etc." is the cases which are specified in APPI, Article 27(1)(ii), (iii) and (iv). For interpretation of APPI, Article 27(1)(ii), (iii) and (iv), see the APPI Guidelines (Common Provisions) and the Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information".

Interpretation of "the case where there is a special need to enhance public health or promote healthy development of children, when it is difficult to obtain consent of the person him/herself" (APPI, Article 27(1)(iii)) is explained in the Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information" as follows:

Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information" (Basic rule of limitation on third party provision)

Q: A medical institution intends to provide a clinical case of its former patient to another medical institution for observational study. When effective contact information is not kept due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the research in view of the time and costs for obtaining consent, is it possible to provide it in absence of consent of said patient?

A A personal information handling business operator shall not provide personal data to a third party in absence of advance consent of the person him/herself; however, when there is a particular necessity in order to enhance public health, and there is a difficulty in obtaining the person's consent, the business operator is allowed to provide personal data to a third party in absence of advance consent of the person (APPI, Article 27(1)(iii)). Medical institutions cannot provide personal data of a patient to other medical institutions which are third parties, in absence of advance consent of the patient.

However, in general, providing clinical cases of a medical institution to another medical institution so as to be utilized in observational studies in said another medical institution or for enhancing medical techniques such as diagnosis and treatment can be considered to especially contribute to enhance public health, because the results of the research are to be widely shared and utilized, or it makes it possible to provide better medical service to unspecified many patients who receive medical services at said another medical institution.

In addition, when medical institutions do not have effective contact information due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the study by obtaining consent from said former patient in view of the time and costs for obtaining consent, it is considered to fall under the case "when it is difficult to obtain consent of the person him/herself".

Therefore, in the case where a medical institution provides personal data of its former patient's clinical case to another medical institution for the purpose of an observational study, when the medical institution does not have effective contact information due to relocation or the like of the former patient, and there is a likelihood of causing impediments in the conduct of the study

by obtaining consent from said former patient in view of the time and costs for obtaining consent, it is considered that the medical institution is allowed to do so according to said provision.
Of note, said another medical institution needs to handle the personal data within the extent of the purpose of use specified at the time of the provision, and thus, in principle, cannot handle the provided personal data exceeding the extent that is necessary to achieve the purpose of use specified as for observational study. In addition, also considering that Article 27(1)(iii) of APPI specifies that personal data can be provided "when it is particularly necessary", the personal data provided by the medical institutions should be limited to just necessary for achieving the purpose of use. Specifically, information such as name and birth date which are not considered necessary for achieving the purpose of use should be deleted or replaced and then provide the minimum necessary information.
Besides, it should be noted that provider and recipient medical institutions are required to comply with the guidelines on medical research, etc., which stipulate involvement of the ethics review committee, ensuring opportunities for human research subjects to refuse, publication of research results, etc., and relevant legal and regulatory provisions.
(Added in June 2021, updated in May 2022)

In (3)B(b) and B(b)(ii), for "academic study purposes", see Section 8-1(1)B(b)(II)(i)a, and for "there is a difficulty in obtaining adequate consent", see the explanation of "when there is a difficulty in obtaining informed consent" of Section 8-1(2).
"When it is necessary to provide the existing samples and special care-required personal information to a collaborative research institution for academic study purposes" and "when ... intends to provide the existing samples and special care-required personal information, it is necessary for the research institution to do the handling for academic study purposes" include the case where a part of the purposes of the provision or handling is for academic study purposes.

9 Regarding (3)A(c) and B(c), opt-out is allowed in the following cases:
(i) there is a difficulty in obtaining informed consent (when providing existing samples and special care-required personal information) or adequate consent (when providing information to be used in research other than special care-required personal information); and
(ii) it is applicable to exceptions prescribed in the items of Article 27(1) of APPI)
When there is a difficulty in obtaining informed consent for existing samples and special care-required personal information, provision may be allowed by notifying to the human research subjects, etc. of the matters of Section 8-6(i) to (v), (viii) and (ix) and then obtaining adequate consent.

10 For "human research subjects, etc., are guaranteed with an opportunity to refuse", see the explanation of Section 8-1(1)B(b)(II)(ii)(opt-out), and for "in principle", see the explanation of Section 8-1(2)A(c)(III).
Of note, the procedures of (3)A(c) and B(c) are to guarantee an opportunity to refuse (opt-out) the provision of existing samples/information in these Guidelines, which is different from the third party provision of personal data by opt-out as set forth by Article 27(2) of APPI. In other words, the procedures of submitting notification to the PIP Commission which are required by said provision are not required here.

In addition, the investigators may, when the requirements of these Guidelines are met, provide samples/information acquired from other research institutions again by opt-out, but, in this case, repetition of acquisition and provision by opt-out is not desired from the perspective of protection of rights and benefits of human research subjects. Thus, whether or not provision by subsequent opt-out is permissible needs to be decided primarily by the principal investigator, and be presented along with the reason thereof to the ethics review committee for review, and then be approved by the head of the research institution.

(4) Procedures for a person who is engaged only in providing existing samples/information

A person who is engaged only in providing existing samples/information shall, in addition to the procedures of (3), fulfill all of the following requirements:

A) The head of the institution to which a person who is engaged only in providing existing samples/information is affiliated shall develop its institutional system and rules which are necessary for properly provide existing samples/information (including the matters relating to the handling of samples/information);

B) A person who is engaged only in providing existing samples/information shall, when providing existing samples/information according to (3)A(a) or B(a)(i) or (b)(i), make the information of the provision of the pertinent existing samples/information available to the head of the institution conducting only the provision of existing samples/information; and

C) A person who is engaged only in providing existing samples/information shall, when intending to provide existing samples/information according to (3)A(b) or (c) or B(a)(ii), (b)(ii) or (c), has obtained approval of the head of the institution conducting only the provision of existing samples/information after receiving opinions of ethics review committee.

1 Section 8-1(4) sets forth procedures for a person who is engaged only in providing existing samples/information.

2 In A, regarding "develop its institutional system and rules which are necessary for properly provide existing samples/information (including the matters relating to the handling of samples/information)", the head of the institution may, for example, develop internal rules of the institution in advance of the provision to other research institutions regarding the handling and procedures (such as how to perform reporting to the head of the institution, how to store records regarding the provision of samples/information). For the records of the provision of samples/information, see explanations of Section 8-3.

3 In B, when providing existing samples/information, if the procedures, etc., of informed consent are not necessary (see the explanation of Section 8-1(3)), it is necessary to make the information of the provision available to the head of the institution that only the head of the institution conducting only the provision of existing samples/information.

4 Regarding C, when providing existing samples/information, if the procedures, etc., of informed consent are necessary (see the explanation of Section 8-1(3)), the provision needs to be reviewed by the ethics review committee and then approved by the head of the institution conducting only the provision of existing samples/information. In C, regarding "after receiving opinions of the ethics review committee", a person who is engaged only in providing existing samples/information may, if necessary, request review by an ethics review committee established in another institution. When requesting opinions of the ethics review committee on adequacy of the provision of existing samples/information, it may be possible to request reviewing in combination with the research protocol, etc., which have been prepared in the recipient institution.

(5) When conducting research using existing samples/information being provided based on the procedures of (3):
The investigators shall, when conducting research using existing samples/information being provided based on the procedures of (3), follow the procedures of A and B below:

A The investigators shall confirm all of the matters listed below:
- (a) contents of the informed consent regarding the existing samples/information or the measures being taken at the time the existing samples/information were provided according to the procedures of (3);
- (b) name and address of the other institution which provided the existing samples/information and full name of the head of said institution; and
- (c) how the existing samples/information was obtained by the other institution which provided the existing samples/information,

B When receiving existing samples/information being provided (excluding the case applicable to (3)A(a) or B(a)(i) or (b)(i)), any of the following requirements is fulfilled:
- (a) when existing individual-related information is provided to conduct research by being applicable to (3)B(a)(ii), perform the procedures according to the provision of (2)B;
- (b) when existing samples/information from which a specific individual can be identified are provided to conduct research by being applicable to (3)A(c) or B(c), place the matters of subsection 6(i), (ii) and (vi) to (ix) in condition readily available to the human research subjects, etc., and, in principle, guarantee an opportunity for the human research subjects, etc., to refuse the conduct or continuation of research,
- (c) when existing samples/information are provided to conduct research by being applicable to (3)A(b) or B(b)(ii), fulfill all of the requirements listed in subsection 9(1) and provide appropriate measures according to subsection 9(2).

1 Section 8-1(5) sets forth procedures of informed consent when conducting research using existing samples/information being provided.

2 Regarding A(a), when the samples/information are to be provided by a person who is engaged only in the provision of existing samples/information, it is preferable to also confirm that the provision is adequately carried out in accordance with the internal rules that apply to the provider's facility.
The purpose of confirming A(b) and (c) is, when it is suspected that existing samples/information to be provided might have not been obtained legitimately, to prevent such samples/information from being used or distributed.
Regarding the case when it is suspected that existing samples/information to be provided might have not been obtained legitimately, for example, when purchasing existing samples/information from a private company (such as a company selling data) or when receiving existing samples/information provided by a person in a foreign state, there may be a case where the recipient is not sure how the provider institution obtained the existing samples/information, etc. In this case, specific contents to be confirmed as "how they were obtained" can vary depending on the specific mode of the third party provision, but, basically, it is necessary to confirm from where the existing samples/information were obtained (e.g., obtained from the person him/herself, another institution, or so-called "open information") and the method of acquisition (e.g., whether they were obtained directly from the person

him/herself, in exchange of money, or from so-called "open information") and so on. However, confirming how the existing samples/information were obtained by the direct provider institution suffices this requirement. It is not necessary for the recipient to confirm how they were obtained prior to the direct provider.

3 Regarding B(a), see the explanation of Section 8-1(3)B(a).

4 In B(b), regarding the obligation to "ensure an opportunity for the human research subjects, etc. to withdraw their consent", it is necessary to provide measures similar to those of Section 8-1(1)B(b)(II)(ii) (i.e., opt-out).
For the meaning of "in principle", see the explanation of Section 8-1(2)A(c)(III).

(6) Handling of samples/information when providing to a person in a foreign state

A When providing samples/information to a person(excluding a person who has established a system meeting the standard set forth in Article 16 of the Enforcement Rules for the Act on the Protection of Personal Information "APPI Enforcement Rules"; the same applies in A and B below) in a foreign state (excluding a state specified by the APPI Enforcement Rules as that applicable to all items specified in Article 15(1) of the same; the same applies hereinafter) (including the case where all or a part of the handling the samples/information are to be entrusted to a person in a foreign state), adequate consent shall be obtained from the human research subjects, etc., on the provision of the samples/information to the person. However, this does not apply to any of the following situations:

(a) when all of the samples/information to be provided are applicable to either (I) or (II) below:

(I) when all of the samples/information (excluding information to be used in research applicable to (II)) are applicable to any of (i) to (iii) below, and the information on the provision of the samples/information is made available to the head of the institution conducting the provision of the samples/information:

(i) in the case where there is a difficulty in obtaining adequate consent, when the samples which are to be provided are in a condition not to be able to identify a specific individual, and personal information will not be acquired in the recipient by using the samples;

(ii) in the case where there is a difficulty in obtaining adequate consent, when the information to be used in research which is to be provided is anonymously processed information; and

(iii) when the information to be used in research which is to be provided is individual-related information (excluding the case where the recipient is presumed to acquire the individual-related information as personal information),

(II) in the case where the information to be used in research which is to be provided is individual-related information (limited to the case where the recipient is presumed to acquire the individual-related information as personal information), when any of the following (i) to (iii) is applicable, or when the person who performs the provision of the individual-related information has confirmed that consent was obtained at the research institution to be the recipient, followed by receiving opinions of the ethics review committee and receiving approval of the head of the institution that performs the provision of the individual-related information:

(i) in the case where it is necessary for a research institution being an academic research institution to provide the individual-related information to a person in a foreign state who is a collaborative research institution for academic study purposes, when there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects;

(ii) in the case where the individual-related information is provided to a person in a foreign state who is an academic research institution, when it is necessary for the recipient to handle it for academic study purposes, and there is no likelihood of causing unlawful infringement of rights and benefits of the human research subjects; and

(iii) in the case where there is a special circumstance in providing the individual-related information, when there is a difficulty in obtaining adequate consent of the human research subjects, etc., in the recipient,

(b) In the case where there is a difficulty in obtaining adequate consent and (a) is not applicable when the phrase "individual-related information" is replaced with

"samples/information" in the provisions of (a)(II)(i) to (iii), when any of (a)(II)(i) to (iii) is applicable, all of the requirements listed in subsection 9(1) are met and appropriate measures according to subsection 9(2) are provided, opinions of the ethics review committee have been obtained followed by approval of the head of the institution that performs the provision of samples/information.

(c) In the case where there is a difficulty in obtaining adequate consent and neither (a) nor (b) is applicable, opinions of the ethics review committee have been obtained on the fact that all of the requirements of the following (I) to (III) are met, followed by obtaining approval of the head of the institution that performs the provision of samples/information.

(I) When the phrase "individual-related information" is replaced with "samples/information" in the provisions of (a)(II)(i) to (iii), any of the requirements (a)(II)(i) to (iii) is met.

(II) Regarding the conduct of the research and the provision of the samples/information to a person in a foreign state, the matters of 6(i) to (v), (viii) and (ix) have been notified to the human research subjects, etc., or placed in a condition readily available to the human research subjects, etc.

(III) Regarding the provision of the samples/information which is to be performed, in principle, an opportunity to refuse is guaranteed for the human research subjects, etc.

B A person who provides samples/information to a person in a foreign state shall, when obtaining adequate consent of the human research subjects, etc., according to A above, provide the information listed below to the human research subjects, etc., in advance:

(I) name of the foreign state

(II) information on the system concerning the protection of personal information in the foreign state which has been obtained by an appropriate and reasonable method; and

(III) information on the measures for the protection of personal information which are to be taken by said person.

C A person who provides samples/information to a person in a foreign state (limited to those who have developed a system meeting the standard set forth in Article 16 of the APPI Enforcement Rules) shall, when (s)he provided samples/information to said person in absence of adequate consent of the human research subjects, etc., take necessary measures for the handling of personal information as required by Article 28(3) of APPI, and provide information on the necessary measures to the human research subjects, etc., upon request of the human research subjects, etc.

1 Section 8-1(6) specifies procedures for providing samples/information to a person in a foreign state (including an business operator such as a research institution or a company that performs testing on commission). When the provision is to a person in a foreign state (including the case where all or a part of the handling of the samples/information is entrusted to a person in a foreign state), it is required to perform the procedures of Section 8-1(6), in addition to any applicable provisions of Section 8-1(1) to (5).

(Reference) Limitation on the provision to a third party in a foreign state under APPI

Under APPI, there are no exception clauses on the limitation on the provision to a third party in a foreign state (APPI, Article 28), similar to those prescribed in the items of Article 27(5) of APPI (provision associated with entrustment, business succession and joint use). When providing personal data

to a third party in a foreign state, in principle, it is required to obtain consent of the person him/herself, whether or not the provision is associated with entrustment or joint use (APPI, Article 28(1)).

2 To provide samples/information to a person in a foreign state, unless either (i) or (ii) below is applicable, in principle, adequate consent of the human research subjects, etc., that acknowledges the provision of the samples/information to a person in a foreign state must be obtained in advance:

(i) said third party is in a state specified by the APPI Enforcement Rules as that having the system for the protection of personal information which is recognized to meet the standard equivalent to that of Japan; or

(ii) said third party has developed a system meeting the standard set forth in Article 16 of the APPI Enforcement Rules.

3 In A, regarding "a foreign state (excluding a state specified by the APPI Enforcement Rules as that applicable to all items specified in Article 15(1) of the same; the same applies hereinafter)", examples of "a state specified by the APPI Enforcement Rules as that applicable to all items specified in Article 15(1) of the same" can be EU and United Kingdom. This is explained in the APPI Guidelines (Provision to Third Parties in Foreign States) as follows:

APPI Guidelines (Provision to Third Parties in Foreign States)

Examples of foreign states having a system on the protection of personal information which is recognized to meet the standard equivalent to that of Japan for the protection of individuals' rights and benefits are EU and United Kingdom. In this context, "EU" refers to the states specified in the "Foreign states, etc., having a system on the protection of personal information which is recognized to meet the standard equivalent to that of Japan for the protection of individuals' rights and benefits " (PIP Commission Public Notice No. 1 of 2019) (however, United Kingdom is excluded).

For details, see APPI Guidelines (Provision to Third Parties in Foreign States), "3 Foreign states having a system on the protection of personal information which is recognized to meet the standard equivalent to that of Japan for the protection of individuals' rights and benefits".

4 In A, regarding "the standard set forth in Article 16 of the APPI Enforcement Rules", Article 16 of the APPI Enforcement Rules set forth as follows:

APPI Enforcement Rules, Article 16

The standard set forth by the APPI Enforcement Rules according to Article 28(1) of the Act is that meets either of the following items:

(1) On the handling of the personal data in a person to be the recipient of the personal data, implementation of the measures in line with the spirit of Chapter 4, Section 2, of the Act has been ensured by an appropriate and reasonable method between the personal information handling business operator and said person to be the recipient; and

(2) the person to be the recipient of the personal data has been accredited based on an international framework on the handling of personal information.

Of note, when it has already been confirmed that the person had developed such a

system, it needs to be clearly described in the research protocol.

In (1), "an appropriate and reasonable method" should be considered and determined on a case basis, but it needs to be a method that can ensure that the person in a foreign state who is the recipient of samples/information continuously take measures equivalent to those that are required to personal information handling business operators in Japan. Examples of such method can be, when the handling of samples/information is entrusted to a person in a foreign state, a written agreement, confirmation or memorandum between the provider and the recipient.

In (2), "accredited based on an international framework on the handling of personal information" means accreditation by a certification authority, etc., based on rules agreed in an international organization, etc., the framework needs to be those which enable to continuously take the measures equivalent to those that are required to personal information handling business operators in Japan. For example, if a person in a foreign state as the recipient has a certificate of the CBPR system of APEC, it suffices the requirement.

For details, see the APPI Guidelines (Provision to Third Parties in Foreign States), "4 Standards for a system necessary for continuously providing measures equivalent to those that are required to personal information handling business operators in Japan".

5 As used in these Guidelines, "adequate consent" means to express one's will of accepting that samples/information of the human research subject are to be provided to a person in a foreign state. Obtaining "adequate consent" means to recognize the will of accepting expressed by the human research subjects, etc., which must be obtained by a reasonable and appropriate method which is necessary for the human research subjects, etc., to make decisions on the consent, taking into consideration the nature of the business and the conditions of the handling of samples/information. For details of "adequate consent", see the explanation of Section 2(23).

6 For "there is a difficulty in obtaining adequate consent", see the explanation of "when there is a difficulty in obtaining informed consent" in Section 8-1(2)A(a)(III).

7 In A(a)(I), regarding "the information on the provision of the samples/information is made available to the head of the institution conducting the provision of the samples/information", similar to the case of Section 8-1(3), for example, the head of said institution formulates institutional rules on the handling, procedures and the like at the time of the provision to the person in a foreign state in advance, and then the person who performs the provision of existing samples/information keeps records on the provision of samples/information based on said institutional rules, or submit reports thereof to the head of said institution.

8 For the provisions of A(a) to (c), see the explanations of Section 8-1(3).

9 Regarding A, to obtain "adequate consent", the human research subjects, etc., must be provided with the information of B(i) to (iii). The provision of information to the human research subjects, etc., must be performed by an appropriate method that is considered to ensure that the human research subjects, etc., can firmly recognize the matters of B(i) to (iii).

(Example)

"We will provide your medical information to XX Academic Association in YY (name of the foreign state) for use in research to elucidate causes and prevalence of ZZ disease.
For information on the protection of personal information in YY (name of the foreign state), please see the following descriptions:
(*Description 1)
In addition, for the measures for the protection of personal information to be taken by XX Academic Association, please see the following descriptions:
(*Description 2)"
*For Description 1, see the explanation of subsection 10 below. *Description 2 needs to be described after confirming with the research institution being the recipient.

10 In B(II), regarding "information on the system concerning the protection of personal information in the foreign state which has been obtained by an appropriate and reasonable method", the PIP Commission making certain information that contributes to the better understanding of inherent differences between the systems on the protection of personal information in certain states or regions and APPI in Japan available to public, aiming at providing information which can be a useful reference for business operators. See the information, as needed, which is available at:
https://www.ppc.go.jp/personalinfo/legal/kaiseihogohou/#gaikoku

11 Regarding B, at the time that "adequate consent" is going to be obtained, if a foreign state where the third party being the recipient is present cannot be identified, information on the following matters must be provided in place of the name of the foreign state and the matter specified in B(II):
- name of the foreign state cannot be identified and the reason thereof (including the necessity of obtaining "adequate consent" prior to the identification of the recipient);
- information to be used as reference by the human research subjects, etc., as an alternative to the name of the foreign state.

In addition, at the time that "adequate consent" is going to be obtained, if it is not possible to provide information on the information on the measures for the protection of personal information which is to be taken by said person, it is required to provide information on that account and the reason thereof in place of the information.
For details, see the APPI Guidelines (Provision to Third Parties in Foreign States), "5 Information provision at the time of obtaining consent".

12 Regarding C, for details, see the APPI Guidelines (Provision to Third Parties in Foreign States), "6 Measures, etc., which should be taken when personal data have been provided to a person who developed a system necessary for continuously providing measures equivalent to those that are required to personal information handling business operators in Japan".

2 Obtaining informed consent by electromagnetic means
The investigators or a person who is engaged only in providing existing samples/information may, obtain informed consent by electromagnetic means, in place of the informed consent in writing according to subsection 1, giving consideration to all of the matters listed below:
(i) performing adequate identity verification of research subjects, etc.;
(ii) ensuring an opportunity for research subjects, etc. to make questions on the contents of the explanation, and fully responding to the questions; and
(iii) making arrangements such that the matters being consented including the matters required to be explained according to 5 are easily viewable after obtaining informed consent, and, in particular, when the research subjects, etc. request, providing these matters in writing.

1 Section 8-2 sets forth matters that require consideration when obtaining informed consent of Section 8-1 by electromagnetic means, which has the same effect as informed consent in writing. This subsection can also be applied, as needed, to research which does not necessarily require obtaining informed consent in writing.

2 The principal investigator is required to review whether or not it is appropriate to obtain informed consent by electromagnetic means and, if it is, a specific method therefor, as well as matters that require consideration such as adequate method of identity verification, according to the contents of the research protocol, and then, seek opinions of the ethics review committee based on the research protocol which clearly shows images such as a screen or video to be presented to the research subjects, etc.

3 Specific methods for giving explanation when obtaining informed consent by electromagnetic means are similar to those for obtaining "adequate consent" or "opt-out" in some points as explained below, but are different in that the former requires to explain all of the "matters required to be explained" of Section 8-5 to obtain consent, and need to meet all of the matters for consideration (i) to (iii).

4 In informed consent, it is possible to carry out the procedure of either giving explanation or obtaining consent by electromagnetic means. In this case, too, it is necessary to meet all of the matters for consideration (i) to (iii).

5 Explanation by "electromagnetic means" means giving explanation by means of electronically or magnetically recorded texts. Specific examples are listed below, but when giving explanation not in person (including when using interactive means such as a TV or phone; the same applies hereinafter), consent shall not be obtained without confirming that the research subjects, etc. have been properly explained and have understood the contents of the explanation.
- meeting in person and displaying the text of explanation or the like on the PC screen for viewing;
- meeting interactively with a video conference call using telecommunication line, and displaying the written document for explanation on the PC screen for viewing.
- sending by email via telecommunication line or posting on the website of the research institution, so that the research subjects, etc. can view; and
- providing an electronic medium such as DVD or USB memory so that the research subjects, etc. can view the text by themselves on their PC, etc.

Explanation needs to be given with written texts, but can also accompany video,

pictures or drawing or contents combining these, for helping the research subjects, etc. to better understand the explanation.

6 Consent by "electromagnetic means" is an alternative method for obtaining consent via telecommunication line, in place of writing. Specific case examples can be checking the check box affixed to the matters required to be explained which are displayed on the PC screen (it does not matter whoever the owner is) and clicking or pressing the consent button, hand-writing a signature on the PC screen, and expressing consent by email, etc.
For research subjects, etc., who are not able to read the texts for explanation or giving consent or who have paralysis, make a creative arrangement with electromagnetic means, and rive consideration such as allowing them to accompany a person who is present and operate the means on behalf of them. The "person who is present" in this context shall be a person who is not involved in the conduct of the research, in order o avoid any inadequate influence from the investigators.

7 In (i), the term "identity verification" means to confirm that the person who performs the procedure is the person him/herself. When the procedure is performed not in person, this means when the investigators performs identity check or identity authentication on the research subjects, etc., which are as exemplified below:

		Specific examples
Identity verification (not in person)	Identity check	- Declaration - Presentation of an ID card, etc.
	Identity authentication	- Single-factor authentication (for example, a method using a single factor such as a password linked to the person's ID). - Multiple-factor authentication (for example, a method combining multiple factors linked to the person's ID, from among "knowledge (password, secret questions, etc.)", "possession" (authentication with SMS or App on a smart phone, sending an email containing one-time password, token, credit card, etc.), and "biometrics" (e.g., face, fingerprint)).

Regarding "performing adequate ...", an adequate level of method of identity verification suitable for the contents or characteristics of the research must be selected. For example, when there are certain risks or burdens such as invasive to the research subjects, if no other identity verification is performed in person at the research cooperative institution, an official ID card (such as "My Number Card", driver's license, passport, or health insurance card) may be checked online. On the other hand, when expected risks or burdens on the research subjects are not so high, such as when the research is not invasive, it may be necessary to give certain considerations for not to impose heavy burdens on the research subjects, such as not to request too much information.
In addition, when selecting a method for requesting to present an ID card, the handling of personal information will require particular care, such as by trying not to obtain personal information more than necessary for the research, and carefully handling their *my* numbers.

8 Regarding "ensuring an opportunity to make questions" in (ii), it is necessary to consider time to be taken by the research subjects, etc. for receiving explanation and understanding the contents of the research. Especially when the procedure is conducted not in person, specific examples can be providing an inquiry form, presenting phone number and email address, etc.
Regarding "fully responding to the questions", it is necessary to obtain consent after the investigators who are the persons who receive informed consent respond to them, and confirm that the research subjects, etc. have understood the contents.

9 In (iii), making arrangements "such that the matters being consented including the matters required to be explained according to subsection 5 are easily viewable after obtaining informed consent" means, specifically, issuing a written document, sending an email, posting on the webpage of the research institution, etc., and making available at the research institution for viewing.

3 Records regarding the provision of samples/information

(1) When providing samples/information

The principal investigator or a person who is engaged only in providing samples/information shall prepare records regarding the provision of the samples/information, and store the records until 3 years have passed from the date of the provision of the samples/information. In a research cooperative institution, a person who is engaged only in providing samples/information shall make the information on the provision available to the head of the research cooperative institution.

(2) When receiving samples/information

When receiving samples/information to be used in the research which are provided by another research institution, the investigators shall confirm that the person who provides said samples/information has completed appropriate procedures and so on, and prepare records regarding the provision of said samples/information.

The principal investigator shall store said records prepared by the investigators until 5 years have passed from the date on which completion of the research is reported.

1 Section 8-3 sets forth matters to be recorded or the like when samples/information are provided and received between collaborative research institutions or between a person who is engaged only in providing samples/information and a research institution. This provision applies to all types of information.

2 The purpose of preparing and storing "records regarding the provision of said samples/information" is to keep records of the provision of information to clarify what, when and to whom the provision was made between the provider institution and the recipient institution, so that the distribution channel can be traced at a later time, in case inappropriate distribution of samples/information occurs. More specifically, the provider institution is required to, referring to Table 1 below, prepare records regarding the provision of samples/information, and store them until 3 years have passed from the date of the provision of said samples/information.
When conducting multi-institutional collaborative research, each of the provider and the recipient collaborative research institutions is required to prepare and store records regarding the provision of samples/information.

3 In (1), regarding "records regarding the provision of the samples/information", for example, it is also possible to prepare an application/report to the head of the provider institution (Form 1) and an application/report to the head of the recipient institution (Form 2) as such records, if the format of which is also suitable as records (see Form 1 and Form 2, in the collection of forms at the end of these Guidelines).

4 In (2), "when receiving samples/information to be used in the research which are provided by another research institution, etc.", it is required to "confirm that the person who provides said samples/information has completed necessary procedures and so on", which means to make sure that the research institution or the institution conducting only the provision of existing samples/information has appropriately completed procedures for the conduct of the research such as informed consent, and, if informed consent or adequate consent has been obtained, the fact and contents thereof need to be confirmed. If information of the research has been notified to or placed in a condition readily available to the research

subjects, etc., and opportunities for rejection have been ensured (by means of opt-out), the fact that the information was notified or placed in a readily available condition and the contents thereof need to be confirmed.
The confirmation needs to be made by an appropriate method such as by way of receiving a statement from the provider institution, specifically, by the following methods, for example:
Case example 1) By way of receiving a verbal statement
Case example 2) By way of accepting mailed documents of a prescribed format
Case example 3) By way of confirming on the website
Case example 4) By way of receiving emails

In addition, it is also possible to request the provider institution to delete unnecessary information before providing a copy of Form 1 (see the collection of forms at the end of these Guidelines).

5 In (2), "preparation and storage of records regarding the provision of samples/information" may be prepared in any format. For example, the provider institution fills out Form 2 (in the collection of forms attached at the end of these Guidelines) and provide it along with the samples/information, and then the recipient research institution confirms the descriptions in the form and stores it. In addition, it is also possible to prepare and store alternative documents such as a copy of the research protocol describing necessary matters or "material transfer agreement (MTA), data transfer agreement (DTA). Some kind of electromagnetic means (e.g., EDC(*), electronic medical records, etc.) may be used for the recording.
* EDC (Electronic Data Capturing): It means collecting research data directly in a form of electronic data without using paper media, or a terminal for collecting research data in such a manner.

6 If records regarding the provision of samples/information are prepared, such records basically need to be prepared at each occasion of the provision, but may also be prepared collectively at the time of mandatory regular reporting according to Section 11-2(5) when a series of acts of the provision has been completed, or at the time of mandatory reporting when the research is completed according to Section 6-6(1). In this case, the research protocol is not required to describe all occasions of expected transfer of samples/information one by one with the identification of the provider institution and the recipient research institution, as long as the contents of a series of transfer of samples/information are described to the extent that the transfer is traceable at a later date.

7 Regarding the provider institution's obligation to prepare and store records explained in point 2 above, if the parties have developed a system that allows to confirm the records upon the provider institution's inquiry to the recipient research institution, the provider institution's obligation of preparing and storing the records can be fulfilled by storing said records at the recipient research institution (however, limited to the case where the matters to be recorded at the provider institution are described in said records). In addition, by ensuring a similar system, the recipient research institution's obligation may be fulfilled by the provider institution on its behalf (in this case, note that the required storage period is different between the provider institution and the recipient research institution).

8 If part of the research works (such as analysis of samples/information) is to be entrusted to an outside vendor such as other domestic corporations or sole

proprietors, between the entrusting institution and the entrusted institution, if they store those that describe required matters (what samples/information are to be provided, how and when they are disposed of, and, in addition, if collaborated among many institutions, name, etc. of the provider institution), such as agreement, pledge, memorandum), they do not need to prepare records regarding the provision of samples/information as set forth in these Guidelines even if they intend to transfer or exchange samples/information.
For descriptions when providing to a person in a foreign state, see the explanations of Section 8-1(6).

4 Amendment of a research protocol The investigators shall, when they intend to amend a research protocol to conduct research, in principle, complete the procedures, etc. according to 1 again to obtain informed consent on the part being amended; provided, however, that this does not apply to a part of amendment which has been approved by the head of the research institution upon consideration of opinions of the ethics review committee.

1 Section 8-4 sets forth procedures, etc. of obtaining informed consent when amending a research protocol. In this case, in principle, procedures, etc. of informed consent according to Section 8-1 must be completed. Any determinations regarding application of said basic provisions should be made primarily by the principal investigator in the process of preparing a research protocol while taking account of the contents of the research and also burdens, etc. of the human research subjects, etc. such as the procedures of informed consent, and be reviewed by the ethics review committee including adequacy of the determination. For an amendment to the research protocol which has been approved by the head of the research institution upon consideration of the opinions of the ethics review committee, explanation may be omitted. For example, change of the principal investigator of one of the collaborative research institutions which plays insignificant role in the research protocol may be an amendment for which explanation is omitted. However, when an explanation is omitted, indication thereof must be included in the amended research protocol and an appropriate consideration should be given in case of a disclosure request by human research subjects, etc. at a later date, so that the research protocol can be disclosed in response to the request.

5 Matters required to be explained

Matters to be explained to the human research subjects, etc. when obtaining informed consent are, in principle, as given below. However, this does not apply to matters approved by the head of the research institution upon consideration of opinions of the ethics review committee:

(i) Title of the research and indication that approval of the head of the research institution for the conduct of the research has been obtained

(ii) Name of the research cooperative institution of the research subject, name of the person who only provides existing samples/information and name of the institution as affiliation of said person, and names of all principal investigators and names of their research institutions

(iii) Objectives and significance of the research

(iv) Method and period of the research (including the purpose of use and handling of the samples/information acquired from human research subjects)

(v) Reason why the person is selected as a human research subject

(vi) Burdens on human research subjects and expected risks and benefits

(vii) Even if the person has given consent to become a subject of the conduct or continuation of research, the consent may be withdrawn at any time (including an indication and reason thereof, if there may be a case where taking measures in accordance with the contents to be withdrawn by the human research subjects, etc.)

(viii) Human research subjects, etc. will not be treated adversely, even if they do not give consent to become a subject of the conduct or continuation of the research or withdraw such consent

(ix) Method of disclosing information relating to research

(x) Upon request of human research subjects, etc., within the extent that does not create hindrance in terms of protecting personal information, etc. of other human research subjects or ensuring creativity of said research, a reference regarding the research protocol and the method of research may be obtained or viewed, and a method for obtaining or viewing the same

(xi) Handling of personal information, etc. (including the method of processing if it is to be processed, and the description of preparing pseudonymously processed information and anonymously processed information if such information is to be prepared)

(xii) Methods of storing and disposing of samples/information

(xiii) Sources of funding regarding the research and any other situations relating to conflict of interest (COI) of the research institution regarding the research, and personal incomes and any other situations relating to COI of the investigators regarding the research

(xiv) Handling of research results, etc., obtained from the research

(xv) Responses to inquiries brought by human research subjects, etc. and people relevant thereto (including genetic counseling)

(xvi) If there is any financial burden on or remuneration to human research subjects, etc., an indication and descriptions thereof

(xvii) If the research involves medical practices beyond the extent of ordinary medical examination, matters concerning other therapeutic methods, etc.

(xviii) If the research involves medical practices beyond the extent of ordinary medical examination, responses regarding the provision of post-research medical care to human research subjects

(xix) If research is invasive, whether or not there is any insurance coverage for compensating health damages caused by the research and descriptions of the

compensation

(xx) With respect to samples/information being obtained from human research subjects, if there is any possibility of use in a future research that is not yet identified at the time of receiving consent from the human research subjects, etc. or there is any possibility of provision to another research institution for such future research, indication thereof and descriptions of expected contents thereof at the time of receiving the consent

(xxi) If the research is invasive (excluding minor invasion) and involves intervention, in the premise that secrets of the human research subject are maintained, persons who are engaged in monitoring or audit and the ethics review committee will view the samples/information relating to said human research subject within the necessary extent

1 Section 8-5 sets forth matters to be explained to human research subjects, etc. when obtaining informed consent. In principle, all items from (i) to (xxi) are required (however, (xvi) to (xxi) are limited to applicable cases). See Section 7, explanations on these items. However, depending on the contents, etc. of research, some items may not always be required. A decision to omit a specific item should be made primarily by the principal investigator, and, the reason for the omission must also be described in the research protocol for review by the ethics review committee and then be approved by the head of the research institution based on "affirmative" opinions of the ethics review committee. A decision on what and how much to be explained should be made by each research institution, taking account of the contents of the research and burdens, etc. of the human research subjects, etc. relating to the procedures of informed consent. When decided to omit, describe what is omitted and why in the research protocol. In this case, give consideration such that the part of the research protocol relevant to the omitted explanation can be disclosed at a later date, in response to a possible disclosure request by human research subjects, etc.
In addition, this is not a closed list of items to be explained. A research institution is recommended to add any items depending on the contents of research, such as ownership of intellectual property rights or other rights on samples/information.

2 Regarding (i), it is also recommended to explain that the research has been reviewed by the ethics review committee.

3 Regarding (ii), for multi-institutional collaborative research, describe name of the collaborative research institution and full name of the principal investigator thereof, and, if the research includes a person who provides existing samples/information at a place other than research institutions, it is preferable to also include full name of said person and name of the institution to which said person is affiliated (if there are many persons, attributes or the like applicable to all of these persons).

4 Regarding (iv), when samples/information are to be provided to another institution (including cases where such provision takes place in connection with outsourcing or sharing), explain about it. For example, when samples/information used in the research will be provided to an institution conducting the collection and provision of samples/information or when data are to be registered to database managed by other institutions, explain about it. In the case of multi-institutional collaborative research, if newly acquired samples/information will be provided to a collaborative research institution, also explain that the provision will take place, along with the

information including what and to where to be provided, the purpose of use, name of the person responsible for the management of the samples/information and the name of the research institution of the responsible person.
If samples/information are to be provided to a person in a foreign state (including the case where such provision will be carried out by an entrusted vendor), in principle, consent on such provision also needs to be obtained according to Section 8-1(6). Thus, if such provision is intended, include explanation thereof to obtain consent. However, as for the description of how to prepare records regarding the provision of samples/information, etc. since it is required to keep records such that distribution channels can be traced later in case of inappropriate distribution of samples/information takes place, it is not necessarily required to be explained to the human research subjects, etc.

5 Regarding (xi), when providing personal information of human research subjects, etc. to another research institution (including cases where personal information is provided in connection with outsourcing or sharing), explanation must include descriptions of the personal information to be provided, name of the research institution as the recipient of the provision, purpose of use in the research institution, name of the person or entity responsible for the management of personal information being provided. The same applies to the handling of samples. In addition, regarding personal information being provided to a collaborative research institution, if a request relating to disclosure, correction, etc., or suspension of use, etc., under APPI has been made by human research subjects, etc., all collaborative research institutions which possess applicable personal information may be required to respond to the request. For details, see the table of Section 2(30) and explanations of Section 18.

6 In the provision of (xii), if cloud service is used in connection with the management of information to be used in research, it is desirable to describe name of the cloud service provider and name of the state where the server storing the information is located. Of note, in this case, how to make public any changes in these contents (such as a place, etc.) should also be explained in advance.

7 For (xiv), see explanations of Section 10-1.

8 Regarding (xv), if there may be a case where a reply cannot be made for the protection of personal information of other human research subjects, etc. or intellectual property rights of the investigator, etc., explanation thereof must be given.

9 Regarding (xvii), "other therapeutic methods" that need to be explained are basically limited to established treatments, but participation in other research projects, etc. may be explained, as necessary. Also, depending on the contents of research, "other therapeutic methods, etc." that are required to be explained may also include an option other than active treatments (such as palliative care and follow-up).

10 Regarding (xx), if there is a possibility of conducting research that is not identified at the time of obtaining consent in the future (including the case of amending the research protocol of earlier research, as well as the case of conducting different research), expected contents of the future research should be explained to the extent possible to obtain informed consent for the earlier research, at least for (ii),

(iii), (iv), (vi) and (xiii). If consent for use in the future research is obtained in this manner, the procedures to obtain informed in the future research may be waived by the procedures according to Section 8-7, i.e., notifying to the human research subjects, etc., or placing in a condition readily available to the human research subjects, etc., and guaranteeing an opportunity to withdraw the consent. Of note, however, this does not mean to accept a so-called "blind trust" by which a broad and vague general power of attorney is given, such as by simply stating "use for medical research". If there is a possibility of providing to a person in a foreign state, in principle, consent on such provision is also required.

10 Regarding (xxi), if investigation is conducted by a regulatory authority, it may confirm information on human research subjects, but such an investigation takes place when there is a serious breach of these guidelines. Therefore, explanation of this item is not a blanket obligation when obtaining informed consent.

6 Matters that should be notified to human research subjects, etc. or made available to the public

In subsection 1, matters that should be notified to the human research subjects, etc. or made available to the public are as follows:

(i) Purpose and method of using the samples/information (if they are provided to another institution, including the method thereof);
(ii) Items of samples/information to be used or provided;
(iii) Name of the institution that provides samples/information and name of the head thereof;
(iv) Method of acquiring the samples/information to be provided;
(v) Name of the principal investigator (representative investigator, in the case of multi-institutional collaborative research) of the research which uses samples/information to be provided and name of the research institution as affiliation thereof;
(vi) Range of people who will use the samples/information;
(vii) Name of the person/corporation responsible for the management of the samples/information;
(viii) Use of samples/information that lead to identify a human research subject or provision thereof to another research institution will be stopped in response to a request made by human research subjects, etc.; and
(ix) Method of receiving the request of (viii) from human research subjects, etc.

1 "Notifying to the human research subjects, etc." means to directly inform to the human research subjects, etc., and, it must be carried out by a rational and adequate method in order to have the human research subjects, etc. recognize the contents of the notice, in view of the nature of the research and actual conditions of the handling of the samples/information.

Case Example 1) Informing by handing over a written document such as a leaflet, etc.
Case Example 2) Informing verbally or by using an auto response device, etc.
Case Example 3) Informing by an email, FAX, etc., or by sending a document by post, etc.

2 "A condition readily available to the human research subjects, etc." means to inform that the research is conducted, widely to the general public (announcing information so that unspecified many people can know it). Means of doing so must be a rational and adequate method, in view of the nature of the research and conditions for handling the samples/information.

Case Example 1) Posting the information at the research institution's website, on the page that its only one click away from the top page.
Case Example 2) Posting a poster, or leaving or distributing pamphlets at a place expected to be visited by the human research subjects, etc. (e.g., medical institution).

3 in (i), "purpose and method of using the samples/information (if they are provided to another institution, including the method thereof)" include an overview of the research (title, purpose, research period, etc.). When notifying or placing in a readily available condition an overview of the research, give consideration such that the range of the human research subjects in the research can be readily clear to any third parties.

When providing to a collaborative research institution or a person in a foreign state

or placing in a condition readily available to unspecified many people, describe the method thereof (such as by recording media, post, electronic transmission, uploading via the internet) so that the human research subjects, etc. can understand.
Regarding "if they are provided to another institution, including the method thereof", when samples/information are to be provided to another institution (including cases where such provision takes place in connection with outsourcing or sharing) or when there is a possibility of entrusting a part of the research, it is necessary to notify thereof to the human research subjects, etc., or place in a condition readily available to the human research subjects, etc. For example, when samples/information used in the research will be provided to an institution conducting the collection and provision of samples/information or when data are to be registered to database managed by other institutions, the method may be notifying thereof to the human research subjects, etc., or placing in a condition readily available to the human research subjects, etc.

4 In (ii), "items of samples/information to be used or provided" mean a common name of the samples/information to be used or provided (for example, blood, hair, saliva, excreta, medical examination data, medical records, etc.), which should include details thereof, to the extent that is necessary to make the human research subjects, etc. understand what kind of samples/information would be used.

5 In (iii), "the institution that provides" means the provider institution.

6 In (vi), "a range of people who will use" refers to names of all collaborative research institutions that conduct the research and names all principal investigators. If there are any persons who are engaged in the provision of existing samples/information other than research institutions, full name of such persons and names of their institutions. If there are too many users to list all of them for the notifying or making public, the following method may be taken alternatively:
- Notifying or placing in a readily available condition name of the representative research institution and name of the principal investigator thereof, along with attributes, etc. common to all people who will use the samples/information, so that the human research subjects, etc. can understand a range of institutions of potential users in the future; or
- When the website or the like of the representative research institution discloses the range of the people, descriptions must indicate the website.

7 In (vii), "name of the person/corporation responsible for the management of the samples/information" means name of the head of the research institution or name of the research institution.

8 In (viii), "use of samples/information that lead to identify a human research subject or provision thereof to another research institution will be stopped in response to a request made by human research subjects, etc." means to guarantee an opportunity for the human research subjects, etc. to refuse that the samples/information associated with the human research subjects are used in the research (or are provided to another research institution).

9 In (ix), examples of "method of receiving the request of (viii) from human research subjects, etc." can be as follows:

Case Example 1) By post
Case Example 2) By email
Case Example 3) By filling out a prescribed form on the website
Case Example 4) By receiving the request at an office
Case Example 5) By phone

10 When notifying to the human research subjects, etc., or placing in a condition readily available to the human research subjects, etc., the following matters may also be included:
- the research protocol and references relating to research methods can be obtained or viewed (including an indication that it is limited to the extent that does not adversely affect protection of personal information of other human research subjects, etc. and intellectual properties, etc.), and methods therefor;
- procedures for disclosure of personal information according to Article 33 of the APPI (including an amount of fee, if it has been specified according to Article 38 of the same);
- if a notice of purpose of use of Article 21 of the APPI), or disclosure of Article 33 of the same or explanation of reason of Article 36 of the same cannot be made, an indication thereof and why; and
- information on how to respond to inquiry, etc. from human research subjects, etc. and people relevant thereto (see explanations in Section 10-2).

7	Procedures for using samples/information in research which was not specified at the time of obtaining consent The investigators shall, in the case where they have explained as much details as possible of the contents that can be expected at the time of obtaining the consent, when a research purpose, etc. has been newly specified subsequently, they shall prepare or amend a research protocol, and notify the information on the contents being newly specified such as the research purpose to the human research subjects, etc., or place it in a condition readily available to the human research subjects, etc., to, in principle, guarantee an opportunity to withdraw the consent for the human research subjects, etc.

1 Section 8-7 sets forth procedures for using samples/information in research which was not specified at the time of obtaining consent. This provision applies on the premise that explanation of purpose of use, etc. expected at the time of obtaining consent from the human research subjects, etc. had been given to the extent possible. Therefore, it is important to note that the application is limited to the case where a new purpose of use, etc. has been specified within the extent of said explanation.

2 The "research which was not specified at the time of obtaining consent" means, for example, in the case where follow-up information of the human research subjects is to be obtained in a prospective cohort study when research is conducted to obtain additional information for a new research purpose, and in research relating to a method of treating a specific disease, when research using collected cells, tissues and information is conducted to analyze relationship with another disease defined after the collection. In these cases, a research protocol must be newly prepared or amended for the new research, and complete procedures in the research institution. Regarding "they shall guarantee an opportunity for the human research subjects, etc. to withdraw the consent", see explanations in Section 8-1(1)B)(b)(II) (opt-out) .

3 The reason why it is specified as "in principle" is that it is expected there may be such a case where rejection is made by the human research subjects, etc. regarding samples/information, but there is a difficulty in identifying and excluding samples/information of he human research subjects, etc. (e.g., only genome data are kept).

8 Handling of research in a situation where there is an immediate and clear danger to the life of the human research subject

The investigators may, if they have found that, according to the procedures as set forth in advance in a research protocol, all of the requirements given below are fulfilled, conduct research without obtaining consent of the human research subjects, etc. However, if said research has been conducted, they shall promptly complete the procedures of informed consent, by means of a written document or electromagnetic means containing the matters required to be explained according to subsection 5:

(i) There is an immediate and clear danger to the life of the human research subject;

(ii) In the case of research involving intervention, when an adequate effect will not be achieved by conducting ordinary medical examinations, it is found that there is a sufficient chance of avoiding the danger to the life of the human research subject by conducting the research;

(iii) Burdens and risks on the human research subject associated with the conduct of the research is within the minimum necessary extent; and

(iv) There is a difficulty in immediately contacting with a proxy consenter or a person who is a proxy consenter to be.

1 Section 8-8 sets forth handling of research in a situation where there is an immediate and clear danger to the life of the human research subject. When performing these procedures, a research protocol must include descriptions thereof as a part of the contents of Section 7(1)(vii) in advance.

2 In (i), regarding "there is an immediate and clear danger to the life", the danger is imminent in terms of time, as well, and it is not expected that the situation does not allow the investigators to complete procedures such as obtaining informed consent from human research subjects nor proxy consenter. Examples of such situation can be severe head trauma, in the state of cardiac arrest, etc.

3 In (ii), regarding "there is a sufficient chance of avoiding the danger to the life", it does not necessarily limit to the case where research for which efficacy has been verified is to be conducted.

9 Simplifying the procedures of informed consent

In the provisions of subsection 1 or 4, when all requirements set forth in (1)(i) to (iv) below are met, and the procedures set forth in (2)(i) to (iii) below can be taken, some of the procedures such as informed consent may be simplified based on the provisions of subsection 1 or 4:

(1) The investigators or persons who are engaged only in the provision of existing samples/information may, when conducting research that fulfills all of the requirements listed below, simplify a part of the procedures as set forth in subsections 1 and 4 above, as prescribed in a research protocol approved by the head of the research institution.
  (i) The research is not invasive (excluding minor invasion);
  (ii) The research does not cause any adverse effects to human research subjects by simplifying the procedures set forth in subsections 1 and 4 above;
  (iii) There is a difficulty in conducting the research or the value of the research will be undermined considerably, if the procedures set forth in subsections 1 and 4 above are not simplified; and
  (iv) The research is found to be socially highly important.

(2) The investigators shall, when simplifying the procedures in accordance with (1), provide appropriate measures from those given below:
  (i) Conducting public relations to the groups including the human research subjects, etc., regarding purposes and contents (including the methods) of the acquisition and use of the samples/information;
  (ii) Providing post incidental explanations to the human research subjects, etc. (including those to the group) promptly; and
  (iii) When samples/information will be collected or used continuously for a long period of time, conducting public relations regarding the actual situations as well as the purposes and methods of the collection and use of said samples/information, and making efforts so that such information can be widely known by the society.

1 Section 8-9 sets forth simplifying the procedures such as informed consent. When simplifying a part of the informed consent procedures, it is necessary to prescribe a reason why all requirements of (1) are fulfilled in the research protocol in advance, as a part of the contents of Section 7(1)(vii).
An example of research for which the procedures can be simplified can be when there is a potential of creating bias in the results of research by informing the purpose of the survey in advance. This provision is intended to apply only to the case where there is a difficulty in conducting the research or the value of the research will be undermined considerably, if the procedures are not simplified.

2 Regarding (1), when the informed consent procedures are simplified according to this provision, the ethics review committee should determine the adequacy of the research from the consideration of weighing up the protection of human research subjects against the outcome obtainable from the research. However, even if the informed consent procedures are simplified, compliance with APPI and legal instruments stipulated by the local government must be ensured. Consistency with APPI and instruments stipulated by the local government, etc. needs to be approved by the head of the research institution, but it is first determined by the principal investigator and then is presented to the ethics review committee along with the reason for the determination, and when the committee gives its opinion that the determination is reasonable, the head of the research institution may approve the

research.

3 In (2)(i), an example of "groups including the human research subjects, etc." can be, when conducting an epidemiological survey on a district where said human research subjects, etc. live, a group consisting of the local citizens in said district. Examples of public relations tools targeted to said group can be circulating a document to all households, posting in a community center, etc. and posting on the website of said group.

4 In (2)(iii), "actual situations" require, for example, making a decision while weighing the necessity and importance against the risks of conducting research for a long period of time without obtaining informed consent, etc.

10 Withdrawal, etc. of consent

The investigators shall, when the human research subjects, etc. have made withdrawal or refusal falling under any of the categories given below, provide measures suitable for the contents being withdrawn or refused and explain thereof to said human research subjects, etc. However, this does not apply to the case where there is a difficulty in providing said measures and the head of the research institution has approved the non-provision of the measures upon consideration of opinions of the ethics review committee. In this case, the investigators must explain to the human research subjects, etc. that they will not provide measures suitable for the contents being withdrawn or refused, and endeavor to explain the reason thereof to obtain understanding from said human research subjects, etc.:

(i) Withdrawal of all or a part of the already given consent to become a subject of the conduct or continuation of research;

(ii) Refusal of all or a part of consent to become a subject of the conduct or continuation of research based on the information being notified or placed in a readily available condition regarding said research (including refusal based on the provision of Section 9-1(1)B)(a)(ii));

(iii) Refusal of all or a part of consent to become a subject of the conduct or continuation of research, expressed in the procedures of informed consent according to subsection 8 above; and

(iv) Refusal of all or a part of consent to become a subject of the conduct or continuation of research, expressed in the procedures of obtaining informed consent from the human research subject, regarding the research for which the proxy consenter has given the consent.

1 Section 8-10 sets forth procedures after consent has been withdrawn or refused. In the case where a person who is engaged in providing existing samples/information has received informed consent or has gave a notification on research to human research subjects, etc. or placed the information in a readily available condition, when the human research subjects, etc. has made a withdrawal or refusal of consent to the a person who is engaged in providing existing samples/information, said person shall promptly inform the fact and the contents of the withdrawal or refusal of consent to the investigators who had provided said existing samples/information.

2 If human research subjects, etc. make withdrawal or refusal of consent to become a subject of the conduct or continuation of research, the withdrawal should be expressed to the investigators in writing. On the other hand, in order to prevent making the human research subjects, etc. feel reluctant to express the withdrawal or refusal by requesting withdrawal in writing, the principal investigator should make an appropriate consideration such as preparing a form for withdrawal or refusal in advance. However, if human research subjects, etc. has orally expressed the will of withdrawal or refusal, the investigators should flexibly respond to said human research subjects, etc. without waiting for a declaration of intent in writing, by promptly taking necessary measures, etc. In addition, unless there is a need of requesting provision of a reason at the time of making a proposal of withdrawal or refusal of consent such as when occurrence of an adverse event is suspected, it is not appropriate to request provision of a reason, as it may have a chilling effect to prevent the human research subjects, etc. from making said proposal.

3 Possible examples of "measures suitable for the contents being withdrawn or

refused" can be discontinuance of the use or disposal of samples/information that have already been obtained by that time, prohibition of the provision of the samples/information to another institution, etc.

4 Examples of the "case where there is a difficulty in providing said measures" can be withdrawal of consent regarding food taken in the body by the conduct of research, and withdrawal of consent regarding the results of research which have already been published as a paper. In these situations, if the head of the research institution has approved the absence of said measures upon consideration of the opinions of the ethics review committee, measures for the withdrawal or refusal of consent may not be necessary, however, it is important to note that the investigators are required to endeavor to obtain understanding of the human research subjects, etc. by explaining the fact of not providing said measures or the infeasibility of said measures and a reason thereof to the human research subjects, etc.

5 When preparing a research protocol, it is necessary to make clear the policies of responses to withdrawal or refusal of consent as a part of the contents of Section 7(1)(vii), and, when receiving informed consent, obtain consent on the response in case of a refusal or withdrawal after giving a sufficient explanation thereof as a part of the contents of Section 8-5(vii). Specifically, if a situation that makes it unable or difficult to provide measures for withdrawal of consent is expected prior to the commencement of the research, this should be explained in the informed consent procedures.
In addition, in research involving invasion, even if withdrawal of consent by the human research subjects, etc. forces to discontinue the research, it is not generally considered to be the "case where there is a difficulty in providing said measures".

6 In (iv), the phrase "procedures of obtaining informed consent from the human research subject, regarding the research for which the proxy consenter has given the consent" is intended to undertake procedures of informed consent from the human research subjects. etc., in such a situation where the research was commenced upon receipt of informed consent from a proxy consenter, when the research is to be continued on the human research subject even after he/she has become competent to give valid informed consent by him/herself (e.g., a situation specified in Section 9-1(3)) (which means when it is expected to continue invasion or intervention on the human research subject or newly acquire samples/information from the human research subject based on the same research protocol).

7 When conducting research involving invasion which is not expected to produce a direct health benefit on human research subjects, if said human research subjects on whom a careful observation has been performed are found to be experiencing an undue pain, it is appropriate to voluntary discontinue the research on said human research subjects, even if said human research subjects, etc. do not express an intention of withdrawal of consent.

Section 9 Procedures, etc. for Obtaining Informed Consent from Proxy Consenters

1 Requirements of consent by proxies

(1) The investigators or a person who is engaged only in providing existing samples/information shall, when they intend to obtain informed consent from proxy consenters in the procedures according to Section 8, fulfill all of the following requirements:

A The research protocol describes all of the following matters:

(i) Policies on selection of proxy consenters; and

(ii) Matters to be explained to proxy consenters (if people who falling into B(a) or (b) are selected as human research subjects, including the reason why it is necessary to select these people),

B Human research subjects fall into any of the following categories:

(a) A minor; however, in the case where the human research subject is a person who has completed the curriculum of junior high school or is a minor of 16 years old or older and is determined to have adequate competence in making a decision on becoming a subject of the conduct of the research, when the research protocol describing both of the following items has been sought for opinions of the ethics review committee on the conduct of the research, and then approved by the head of the research institution, informed consent shall be obtained from the human research subject instead of a proxy consenter:

(i) The conduct of the research is not invasive; and

(ii) Information on the conduct of the research including objectives of the research and the handling of samples/information is to be placed in a condition readily available to the person with custody or the guardian, etc., and an opportunity to refuse to have conducted or continued the research is to be guaranteed for said person.

(b) An adult, who is objectively determined to be incompetent in giving valid informed consent.

(c) A dead person, excluding the case where becoming a subject of the conduct of the research is against the dead person's explicit will before the death.

(2) The investigators or a person who is engaged only in providing existing samples/information shall, when obtaining informed consent from proxy consenters in the procedures of Section 8, select proxy consenters in accordance with the selection policies of (1)A)(i), and explain to the proxy consenters the matters prescribed in (1)A)(ii) as well as the matters prescribed in Section 8-5.

(3) The investigators or a person who is engaged only in providing existing samples/information shall, when they have obtained informed consent from a proxy consenter, if the human research subject has completed the curriculum of junior high school or is a minor of 16 years old or older and is determined to have adequate competence in making a decision on becoming a subject of the conduct of the research, obtain informed consent also from the human research subject.

1 Section 9-1 sets forth requirements to be fulfilled, matters to be observed, etc., when the investigators or a person who is engaged only in providing existing samples/information intend to obtain informed consent from proxy consenters.

2 In (1)A(i), regarding "policies on selection of proxy consenters", in general, proxy

consenters should be selected from the persons listed in (i) to (iii) below, in principle:

(i) (When the human research subject is a minor) the person with custody or the guardian
(ii) Spouse, parent, sibling, child/grandchild, grandparent, relative living in the same household of the human research subject, or a person whom can be considered as having a similar relationship to the foregoing (excluding a minor)
(iii) An attorney of the human research subject (including a voluntary guardian with power of attorney)

However, instead of selecting based on uniform and fixed standards, specific situations of each individual human research subjects should be taken into account, for example, an emotional relationship such as a partner or trust relationship with the human research subject, and, in some cases, a possibility of abuse against the human research subjects, etc., and, based on such consideration, a person who is capable of representing will and interest of the human research subject should be selected. Also, when informed consent is received from proxy consenters, it is important to keep records that show relationships between these persons and the human research subjects.

3 In (1)A(iii), regarding "the reason why it is necessary to select these people", it is not appropriate to obtain samples/information which can be reasonably obtained from human research subjects who are competent to give informed consent on their own from persons who are incompetent in giving valid informed consent. It is important to note that adequacy of conduct based on informed consent obtained from proxy consenter is recognized, basically, only in the research on the events uniquely found in a group of the human research subjects (such as infants, persons with mental disabilities, persons who are in nursery home, etc.).

4 In the case where research was commenced based on informed consent obtained from a human research subject and said human research subject has become incompetent in giving valid informed consent due to injuries and diseases, etc., when the research has been continued on said human research subject or when handling of samples/information which had been obtained from said human research subject are to be changed, an appropriate proxy consenter must be selected according to Section 9-1(1) and (2) and procedures to obtain informed consent from the proxy consenter must be performed. In addition, it is important to note that, due to (1)A(iii), there is a promise that the reason why a person who is objectively determined to be incompetent in giving valid informed consent needs to be kept as the human research subject is described in the research protocol in advance, thus, this is limited to the case where the conduct of said research has been approved by the head of the research institution upon consideration of the opinions of the ethics review committee.

5 In (1)B(a), "minor" is interpreted according to the Civil Code in Japan, which is "a person who is under 18 years old and have not married yet" prior to April 1, 2024, or "a person who is under 18 years" on or after said date.

6 In (1)B(a) and (3), the phrase "completed the curriculum of junior high school" is intended to mean the curriculum of junior high school in the Japanese educational system. If a human research subject has completed the curriculum of junior high school abroad, basically, the requirement of 16 years old or older applies. The term "junior high school" encompasses a special school corresponding to a junior high

school.

7 In (1)B(a) and (3), regarding the phrase "is determined to have adequate competence in making a decision on becoming a subject of the conduct of the research", if a minor who has completed the curriculum of junior high school or is 16 years old or older is determined to be experiencing healthy emotional development and be healthy in terms of emotional state, it may be basically determined that the minor has adequate competence in making a decision on becoming a subject of the conduct of the research. However, as for research involving invasion, such a human research subject is not able to give valid informed consent by him/herself alone, and it is necessary to obtain informed consent from a proxy consenter such as the person with custody and then obtain informed consent also from said human research subject in accordance with (3).
In the case where research was commenced based on informed consent obtained from a proxy consenter of a minor human research subject and subsequently he/she has completed the curriculum of junior high school or has become 16 years old and has been determined to have adequate competence in making a decision on becoming a subject of the conduct of the research, when the research is to be continued on said human research subject, informed consent must be obtained from said human research subject. However, this does not apply to the case where samples/information which has already been obtained from said human research subject based on the consent obtained from the proxy consenter are to be analyzed, etc. within the scope of said consent.

8 In (1)B(a)(ii), in "the person with custody or the guardian, etc. for minors", "etc." can be the director of a child welfare institution, the director of a foster home institution, and foster parents.

9 In (1)B(b), regarding "an adult, who is objectively determined to be incompetent in giving valid informed consent", considering that a consensus on the definition of a power or right of a guardian of adult to give consent on medical services has not reached yet among legal experts, if a guardian of adult, a curator, etc. has been appointed for a human research subject with respect to medical practices for a research purpose, in particular, a medical practice exceeding the extent of ordinary medical examination which is performed for a research purpose or is not expected to produce a direct health benefit on the human research subject (such as blood sampling or drug administration which is not for prophylaxis, diagnosis or treatment of injuries and diseases), a decision as to whether selecting a proxy consenter from those persons is appropriate should be made very carefully.

10 It is not appropriate to immediately determine that a person is incompetent in giving valid informed consent simply based on the fact that a guardian of adult, a curator, etc. has been appointed for said person, and the decision should be made taking also account of contents of research to be conducted or continued (such as whether there are any burdens on human research subjects and expected risks and benefits, and contents thereof) as well as the condition of the each individual human research subject.
In addition, regardless whether a person is determined to be incompetent in giving valid informed consent, a person for whom a guardian of adult, a curator, etc. has been appointed is generally considered to be in the group of "socially vulnerable people" of Section 1(vi). Thus, a decision of adequacy to select such a person as a

human research subject should be carefully made and special considerations should be given.

11 In (1)B(b), a typical example of "an adult, who is objectively determined to be incompetent in giving valid informed consent" can be a patient who is unconscious due to an injury of disease and a person who is in coma. However, it is not appropriate to immediately determine that a person is determined to be "incompetent in giving valid informed consent" based solely on the fact that he/she has been diagnosed with dementia or schizophrenia, etc. Instead, such a determination should be made taking also account of the contents of research to be conducted or continued (such as whether there are any burdens on human research subjects and expected risks and benefits and contents thereof) as well as the condition of each individual human research subject. The phrase "who is objectively determined" means that even a person who is not involved in the research (not necessary a physician) can also find the same, which should be confirmed by, for example, at least two medical personnel or care workers (it is preferable if their occupations are different from each other), or based on discussion with a person qualified to be a proxy consenter (such as family members) or in cooperation with local caseworkers, etc. If there are any guidelines, etc. presented by an academic association, professional association, etc. in the relevant field, such materials should be referred to and reflected in the research protocol, taking account of the contents of the research.
In the case where research was commenced based on informed consent obtained from a proxy consenter of a human research subject who falls into the scope of (1)B(b) and subsequently he/she becomes no longer applicable to (1)B(b) (i.e., he/she has become competent to give valid informed consent), when the research is to be continued on said human research subject, informed consent must be obtained from said human research subject. However, similarly to the explanation in 9 above, this does not apply to the case where samples/information which has already been obtained from said human research subject based on the consent obtained from the proxy consenter are to be analyzed, etc. within the scope of said consent.

2 Procedures when obtaining informed assent

(1) The investigators or a person who is engaged only in providing existing samples/information shall, when they have obtained informed consent from a proxy consenter, if the human research subject is determined to be capable of expressing his/her own will with respect to his/her becoming a subject of the conduct of the research, endeavor to obtain informed assent; provided, however, that this does not apply to the case where informed consent is obtained from the human research according to subsection 1(3) above.

(2) The principal investigator shall, when he/she intends to conduct research that is expected to involve the informed assent procedures under (1) above, describe the matters required to be explained to be given to the human research subjects and how to provide explanations to them in a research protocol in advance.

(3) The investigators and a person who is engaged only in providing existing samples/information shall, when the human research subject has expressed his/her intention to refuse to give all or a part of the consent to become a subject of the conduct or continuation of the research in the informed assent procedures under (1) above, endeavor to respect such will. However, this does not apply to the case where it is expected that the human research subject will receive a direct health benefit by becoming a subject of the conduct or continuation of the research and his/her proxy consenter gives consent thereto.

1 Section 9-2 sets forth matters to be complied with, etc. when the investigators or a person who is engaged only in providing existing samples/information are required to endeavor to obtain informed assent or when the investigators or a person who receives provision of existing samples/information obtain informed assent.

2 In foreign countries, the term "assent" or "informed assent" is often used in cases where children are to be selected as human research subjects. However, these Guidelines do not limit the scope to children, so as to encompass the case where human research subjects are not able to give valid informed consent due to injuries, diseases, etc.

3 In (1), the phrase "if the human research subject is determined to be capable of expressing his/her own will with respect to his/her becoming a subject of the conduct of the research" means the state that a person is able to understand language and express his/her own will based on the rational thought, and, for example, when minors under 16 years old are selected as human research subjects, it is preferable that considerations are given taking account of the development of each of the human research subjects. Also, Q&A (June 22, 2001, Administrative Communication of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) for the guidance for clinical trials of pharmaceutical products in the little children population which has been agreed in ICH provide a rough standard of the age when obtaining assent from human subjects of little children, which is approximately 7 years old or older (approximately a junior high school student or older, for assent in writing), by reference to the Guidelines published by the American Academy of Pediatrics. The guidance may be used as a reference where applicable, depending on the contents of research.

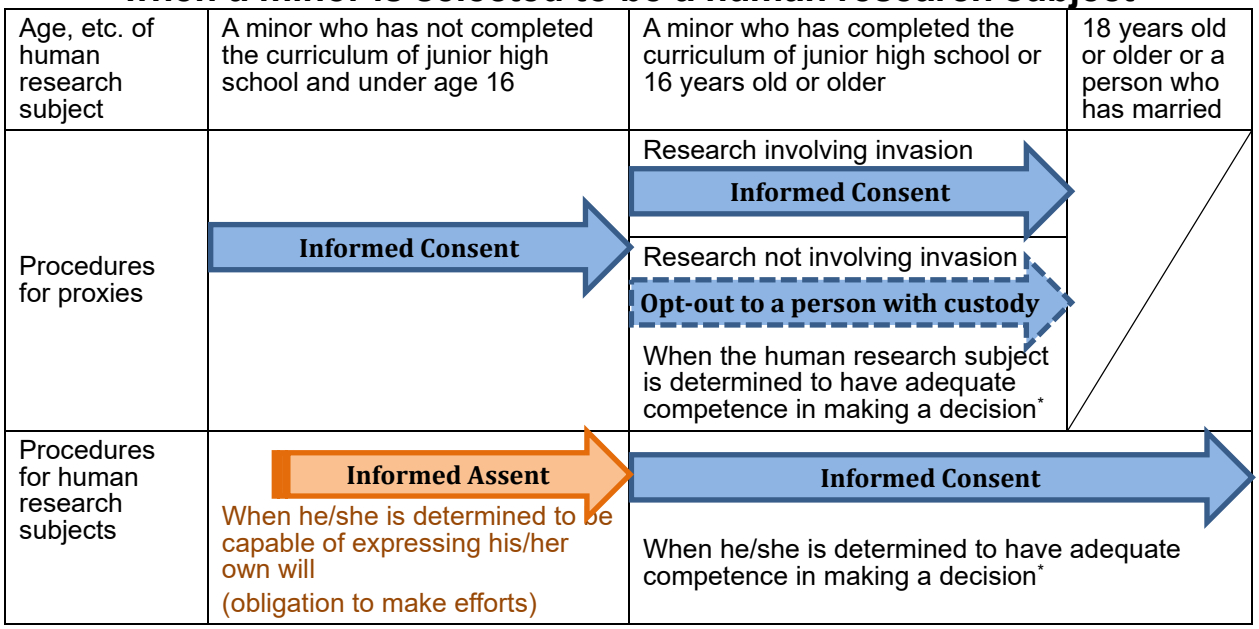
4 In the case where research was commenced based on informed consent obtained

from a proxy consenter of a minor human research subject and subsequently he/she is determined to become capable of expressing his/her own will with respect to his/her becoming a subject of the conduct of the research, when the research is to be continued on said human research subject, the investigators are required to endeavor to obtain informed assent from said human research subject. Also, in the case where research was commenced based on informed consent obtained from a proxy consenter of a minor human research subject, when handling of samples/information which had been obtained from said human research subject are to be changed, the investigators are required to perform the procedures of informed consent for said proxy consenter again and endeavor to obtain informed assent from said human research subject.

5 Regarding the matters required to be explained to human research subjects in the procedures of informed assent of (2), the investigators should endeavor to explain those that can be understood by the human research subjects, among those specified as the matters required to be explained in the research protocol when obtaining informed consent.
Also, regarding a method of giving explanation to the human research subjects in the procedures of informed assent, besides using plain, easy-to-understand expressions, it is preferable to use documents with illustrations, figures and tables and give considerations to the time necessary for understanding the contents, taking account of the human research subjects' ability to understand.

6 When informed consent is obtained from a proxy consenter and informed assent is not obtained from the individual human research subject in view of the intellectual maturity of said subject, it is still preferable to explain any matters relating to the research to be conducted or continued on said subject if those matters are considered to be understandable to said subject.

Informed consent and informed assent when a minor is selected to be a human research subject



*When human research subjects is determined to be incompetent in making a decision on his/her becoming a subject of the conduct of research, informed consent must be obtained from a proxy consenter. Then, when it is found that the human research subject is capable of expressing his/her own will, informed assent must be obtained from said human research subject (obligation to make efforts).

Chapter 5 Handling of Results, etc. Obtained from Research
Section 10 Explanation of Results, etc. Obtained from Research

1 Procedures, etc. relating to explanation of results, etc. obtained from the research

(1) The principal investigator shall, taking account of the characteristics of research to be conducted and results, etc. obtainable from the research, prescribe policies on how to explain results, etc. obtainable from the research to research subjects, and describe them in the research protocol. When prescribing the policies, the principal investigator shall consider the following matters:
   A whether the results, etc. have sufficient level of accuracy and certainty as information for evaluating health conditions, etc. of the research subjects;
   B whether the results, etc. are important facts for health, etc. of the research subjects; and
   C whether explanation of the results, etc. has a possibility of causing a detrimental impediment to proper conduct of the research works.

(2) The investigators shall, when obtaining informed consent from research subjects, etc., explain the policies on how to explain results, etc. obtained from the research of (1), and obtain understanding from them. Then, if the research subjects, etc. do not desire explanation of the results, etc. obtained from the research, the investigators shall respect the will. However, the investigators shall, even when the research subjects, etc. do not desire explanation of the results, etc. obtained from the research, if it has been found that the results, etc. have serious impacts on the lives of the research subjects, their blood relatives or the like, and there are effective responsive methods, report thereof to the principal investigator.

(3) The principal investigator shall, upon receipt of the report of (2), consider whether the explanation should be given to the research subjects, etc., how and what should be explained to them, taking account of the following perspectives, and seek opinions of the ethics review committee:
   (i) impacts on the lives of the research subjects and their blood relatives and the like;
   (ii) whether there is an effective therapeutic method, and health conditions of the research subjects;
   (iii) whether there is a possibility that blood relatives and the like of the research subjects are affected with the same disease, etc.;
   (iv) what are the contents of the explanation on the research results, etc. at the time of obtaining informed consent.

(4) The investigators shall, taking into consideration the opinions of the ethics review committee of (3), give adequate information to the research subjects, etc., and confirm the intention of the research subjects, etc., but shall not give explanation if explanation is not desired.

(5) The investigators shall not explain without consent of the research subjects, etc. about results, etc. obtained from the research on the research subjects to a person other than the research subjects, etc., in principle. However, this does not apply to the case where the research subjects' blood relatives or the like desire explanation on the results, etc. obtained from the research, and the principal investigator has sought opinions of the ethics review committee on whether it is acceptable to explain in view of the reason why they request explanation and necessity of explanation, and has decided that the explanation is necessary.

1 Section 10-1 sets forth matters to be considered when explaining results obtained

from each research and information relating thereto to the research subjects. Matters related to disclosure or the like of personal information are set forth in the APPI and the provisions set forth by local governments, which need to be considered separately from the provisions explained in this section. For details, see the explanations in Section 18.

2 Regarding (1), the "results, etc. obtainable from the research" include not only the primary results which were originally aimed at elucidating in the research protocol and observations, but also secondary results obtained in association with the conduct of the research and observations (so-called "incidental finding"). In any case, policies on how to explain the results, etc. to the research subjects, etc. need to be decided at the stage of planning the research protocol, according to this section, and then explain those policies to the research subjects, etc., and obtain their understanding. Of note, the term "incidental finding" means information (such as being affected with cancer or a genetic disease) that may have a serious impact on the life of the human research subjects and has been found in the process of conducting research. The term "handling of research results" includes policies on disclosure of research results, method of disclosure, etc.

3 In (1), the "policies on how to explain ... to research subjects" include, for example, when analyzing the whole genome sequence of an individual, information which does not have sufficient levels of accuracy and certainty as information for evaluating health conditions or the like of the research subjects, etc., thus, it is difficult to explain all genetic information including such information. Therefore, it is necessary to give adequate consideration such as limiting the explanation to the part that can be certainly used to evaluate health conditions, etc. of the research subjects, so that the conduct of adequate research will not be affected.
When deciding policies on specific cases, it is necessary to give considerations to the fact that specific contents of the results and the impacts on the research subjects vary on a case basis depending on the purpose and method of the research, and make decisions objectively and carefully, while also taking account of common sense.

4 In (2), regarding "the results, etc. have serious impacts on the lives of the research subjects, their blood relatives or the like", examples thereof include, when results of gene analysis research show that the research subject has a disease which is highly probable to be occurred in the family and is likely to have serious impacts on the lives of them, and when the results reveal that the research subject is affected with a specific infectious disease and it is necessary to prevent spread of the disease for the sake of public health, etc.

5 Regarding (4), taking account of the conclusion of the ethics review committee in (3), necessary results, etc. are to be explained to the research subject, the principal investigator needs to make efforts to obtain understanding of the research subjects again to obtain consent on the provision of necessary information to the people who are considered to be influenced.

6 Regarding (5), when consent on the conduct of the research has been obtained from the proxy consenter, the investigators may explain results, etc. obtained from the research to the proxy consenter upon request. On the other hand, when the consent on the conduct of the research was obtained from the research subject

him/herself but the consent on giving explanation to a person other than the research subject has not been obtained, if explanation of results, etc. obtained from the research is demanded individually by a blood relative of the research subject, the investigators need to seek opinions of the ethics review committee.
When a research subject is a minor and is 16 years of age or older, in order to give explanation to the proxy consenter, the will of the research subject must be confirmed and respected.

7 The investigators shall, when there is a concern about possible consequences of giving explanation on the minor's genetic information, such as the research subject's self-injurious behavior, discrimination against the research subject, rejection of caring, and adverse effects on the treatment, report the concern to the principal investigator. The principal investigator shall, prior to the explanation of the results, seek opinions of the ethics review committee or conversation between the minor and the proxy consenter, as needed, and decide whether or not explanation of the results should be made, and what and how should be explained.

2 System for responding to inquiries, etc. regarding research The principal investigator shall, when handling results, etc. obtained from the research, while taking fully into consideration medical or psychological effects or the like in view of the characteristics of results, etc., develop a system that allows to suitably respond to inquiries from the research subjects, etc. regarding the research. The principal investigator shall take priority in maintaining close cooperation with medical doctors who take charge of medical treatment in developing the system, and, when handling genetic information, shall endeavor to ensure cooperation with persons who conducts genetic counseling and medical genetics experts.

1 Section 10-2 sets forth matters to be considered by the principal investigator when developing a system for responding to inquiries, etc. for each individual research.

2 The principal investigator should expect a wide range of "inquiries regarding research", such as those relating to the conduct based on an individual research protocol or procedures for conducting the research, those relating to results, etc. obtained from the research. Among them, counseling on the diagnosis or treatment takes place during medical practices, and thus, the system needs to allow immediate cooperation with medical doctors. In conducting research, the principal investigator needs to make a system for responding inquires such as by setting up a contact office for receiving inquires in the research.

3 In an institution providing samples/information, when a system for counseling not been established, when research subjects and their families or blood relatives requested counseling, they should be referred to an appropriate institution for that purpose.

4 In genetic counseling, the principal investigator is required to maintain close cooperation with clinical medical genetics experts, certified genetic counselors, etc., and arrange multiple sessions of counseling, as needed.

Chapter 6 Ensuring Credibility of Research
Section 11 Appropriate Response in Research and Reporting

1 Ensuring ethical validity and scientific rationality of research

(1) The investigators shall, when upon knowing any fact or obtaining information which is considered to ethical validity or scientific rationality of research (excluding the case falling into (2) below), promptly report it to the principal investigator.

(2) The investigators shall, when knowing any fact or obtaining information which is considered to undermine integrity of the conduct of research or credibility of research results, promptly report it to the principal investigator or the head of the research institution.

(3) The investigators shall, when any serious concern arises from the viewpoint of respecting human rights of human research subjects, etc. or appropriate conduct of research, such as divulgence of research-related information, promptly report it to the head of the research institution and the principal investigator.

1 Section 11-1 sets forth what the investigators should comply with in order to adequately conduct research and an obligation of reporting when certain information has been known to them.

2 In (1), a fact that undermines "ethical validity of research" means, in the conduct of the research, a defect of procedures of informed consent, inadequate handling of personal information, etc., and facts to be adequately handled in the conduct of research from the perspectives of protection of human rights and consideration of welfare of human research subjects. A "fact that undermines scientific rationality" means, regarding said research, a fact that may change the overall assessment of burdens and expected risks and benefits to be incurred by human research subjects which have been described in the research protocol by the principal investigator before the commencement of the research, due to finding of new scientific knowledge or contents which have been revealed after the commencement of the research, information of safety measures implemented by a domestic or foreign regulatory authority, etc. Further, "information that may undermine" means such information that has not been determined to be true, after it has been known.

3 In (2), a fact or information that undermines "integrity of the conduct of research" means, in the conduct of the research, a fact or information of such as deviation from the selection policies of human research subjects or research methods based on the research protocol. Also, a fact or information "that erodes trust in research results" means a fact or information such as falsification or fabrication of research data. Further, "information that may undermine or erode the same" means information that has not been determined to be a definite fact since such contents were known. In addition, when a report is made to the principal investigator, if there is a concern of disguise by said principal investigator, the head of the research institution must be reported directly.

4 In (3), examples of "when any serious concern arises from the viewpoint of respecting human rights of human research subjects, etc. or appropriate conduct of research" may be, besides "divulgence of research-related information", when information that may influence continuance of research has been known, such as when a voluntary decision-making of human research subjects on participation in

the research was restricted or a serious adverse event has occurred.

5 In (3), regarding "divulgence, etc., of research-related information", the term "divulgence, etc." refer to divulgence (which means letting information leak out of the institution), loss (which means losing the contents of the information) or damage (which means causing unintentional alteration of the contents of the information or resulting in a condition that the contents are kept but can no longer be used). The term also includes divulgence, etc. at the entrustee. The head of the research institution shall, when a case of divulgence, etc. (a case of divulgence, etc. or likelihood of divulgence) has arisen, seek for opinions of the ethics review committee, and provide necessary responses (including reporting, etc., to Ministers, as set forth in Section 11-3, when the degree of noncompliance is determined to be serious). Of note, the head of the research institution needs to, when a case of divulgence, etc., which requires mandatory reporting as prescribed by Article 7 or Article 43 of the APPI Enforcement Rules has arisen, report the occurrence of the case to the PIP Commission based on Article 26 or Article 68 of APPI, and notify, etc., thereof to the person him/herself.
As for information of a dead person, if a possible impact on kin family cannot be denied, such as when the information applicable to special care-required personal information has been divulged, the kin family needs to be notified, etc.

2 Management and supervision of progress of research and understanding and reporting adverse events, etc.

(1) The principal investigator shall endeavor to ensure appropriate conduct of research and reliability of research results, such as by collecting information necessary for the conduct of research.

(2) The principal investigator shall, when the reporting of subsection 1(1) above being received is considered to influence the continuation of research (excluding the case falling under (3)), report it to the head of the research institution without delay, and, if necessary, suspend or discontinue the research or amend the research protocol.

(3) The principal investigator shall, upon receipt of the reporting of subsection 1(2) or (3) above, promptly report it to the head of the research institution, and, if necessary, suspend or discontinue the research or amend the research protocol.

(4) The principal investigator shall, in the conduct of research, when expected risks are found to outweigh the potential benefits or when it is found that sufficient results have been obtained or would not be obtained, discontinue the research.

(5) The principal investigator shall report the progress of the research and any adverse event occurred in association with the conduct of the research to the ethics review committee and the head of the research institution, as specified in the research protocol.

(6) The principal investigator shall, when conducting multi-institutional collaborative research, share necessary information relating to the research with the principal investigators of the collaborative research institutions.

(7) The head of the research institution shall, upon receipt of the reporting of any of subsection 1(2) or (3) or 2(2) or (3), seek opinions of the ethics review committee, as necessary, and, respecting the opinions being given, promptly take appropriate responsive measures such as suspending the research or determining the root cause. In this case, the head of the research institution shall, prior to receiving opinions of the ethics review committee, give instructions to the principal investigator, as necessary, for suspension of the research or other provisional measures.

1 Section 11-2 sets forth responsibilities of the principal investigator, including making a decision of continuation, discontinuation or the like of research during the research period, submitting a mandatory report to the head of the research institution, etc.

2 Regarding (1), before the completion of the research, the principal investigator should continuously gather information that have been made available in Japan and abroad through presentations in academic conferences, publications on journals, etc. (hereinafter, "published information") which is necessary to estimate risks and ensure safety in the conduct of the research, and any information available at hand falls into the case of (2), report it to the head of the research institution.
When the research is to be conducted in cooperation with another research institution, the principal investigator should share the published information at hand with the principal investigator of the collaborative research institution according to (6).

3 In (1), examples of "endeavor to ensure appropriate conduct of research and reliability of research results" can be, besides "collecting information necessary for the conduct of research", performing monitoring suitable for the contents of the

research, performing audit as necessary, and storing samples/information, etc.

4 In (2), the principal investigator is, when the information has been obtained, required to determine whether or not it influences the continuation of research, and voluntary take necessary responsive measures without waiting for measures taken by the head of the research institution according to (7).

5 In (2), "without delay" means without causing an unreasonable delay, giving consideration that a certain time period may be needed for the determination.

6 regarding (3), the principal investigator is required to promptly report the information to the head of the research institution, and also voluntary take necessary responsive measures without waiting for measures taken by the head of the research institution according to (7).

7 In (4), regarding the phrase "when expected risks are found to outweigh the potential benefits", the principal investigator is required to continue overall assessment of burdens on human research subjects and expected risks and benefits which was made prior to the commencement of the research until the completion of the research, by scrutinizing the facts and information being reported by other the investigators according to Section 11-1(1), a serious adverse event reported according to Section 15-1 and also information necessary for the conduct of the research which has been collected by him/herself according to (1).

8 In (4), when it is found that "sufficient results have been obtained" means, for example, when the intended number of cases prescribed in the research protocol has been reached in the middle of the research period, whereby the research purpose described in the research protocol has been achieved, etc. In addition, the term "sufficient results" includes the case where the results do not necessarily support the hypothesis. In other words, when continuing the research, the principal investigator is required to make determinations as to whether the purpose of the research has been achieved, or whether it is clear that the purpose will not be achieved by further continuing the research.

9 In (5), regarding "progress of the research and any adverse event occurred in association with the conduct of the research", if any research cooperative institution is involved in the research, information needs to be obtained from said institution as well.

10 Regarding (5), a report should be made in writing at least once a year in principle, but, depending on the contents of research, any interval such as once in three years may be prescribed taking into account the characteristics of the research. However, even in such a case, when and with what interval reports should be made must be prescribed in the research protocol and mandatory regular reporting will not be waived.

11 In (5), typical examples of the matters to be reported are as follows:
- progress of the research (including number of cases studied, number of analyzed samples/information, etc.);
- whether or not adverse events or any other problems have occurred, and statuses thereof;

- method of storing samples/information; and
- status of provision of samples/information to other institutions.

12 Regarding (6), when conducting multi-institutional collaborative research, a representative investigator is appointed, but this does not mean that the sharing of information must be done by the representative investigator him/herself. it is recommended to clearly identify offices for sharing necessary information relevant to the research (including serious adverse events), such as by establishing a secretariat for the research, so that such information can be shared smoothly between principal investigators of collaborative research institutions. Also, the principal investigator should describe in the research protocol roles for promoting adequate and smooth conduct of the research in cooperation with principal investigators of the collaborative research institutions as a part of the institutional system to carry out the research.

3 Reporting, etc., to Ministers

(1) The head of the research institution shall, when he/she has become known to the fact that research that has or had been conducted by the research institution does not comply with these Guidelines (including by means of the reporting of any of subsection 1(2) or (3) or 2(2) or (3)), promptly seek and receive opinions of the ethics review committee and provide necessary responses, and, if it is a serious incompliance, report the details and results of the responses being taken to the Minister of Health, Labour and Welfare (or for a research institution controlled by MEXT, the Minister of Education, Culture, Sports, Science and Technology and the Minister of Health, Labour and Welfare, or for a research institution controlled by METI, the Minister of Health, Labour and Welfare and the Minister of Economy, Trade and Industry; hereinafter, simply "Minister") and make it available to the public.

(2) The head of the research institution shall cooperate with inspections and investigations conducted by the Minister or an entrustee thereof (hereinafter, "Minister, etc.") to make sure that research in the research institution complies with these Guidelines.

1 Section 11-3 sets forth responsibilities of the head of the research institution and measures to be taken when a serious incident which does not comply with these Guidelines has occurred in research conducted in the research institution, or the like.

2 Regarding (1), since there are a wide range of contents of research which are within the scope of application of these Guidelines, a determination whether or not it is "a serious incompliance" should be made on a case basis, after hearing the opinions of the ethics review committee, in terms of how severely deviated from these Guidelines and whether it is to the extent that undermines ethical validity and scientific rationality of the research.
However, the cases as exemplified below are considered to be a serious incompliance regardless of the contents of the research, thus, must be reported to the Minister and must be made available to the public:
- The research has been commenced without being reviewed by the ethics review committee or without obtaining approval of the head of the research institution;
- The research has been commenced without completing necessary informed consent procedures;
- A fabrication or falsification of research results which undermines credibility of the contents has been discovered; and
- A report of "divulgence, etc., of research-related information" of subsection 1(3) has been received.

3 In (1), "a research institution controlled by MEXT" can be a university or a corporation such as an independent administrative corporation controlled by MEXT. "A research institution controlled by METI" can be a corporation such as an independent administrative corporation controlled by MEXT.

4 Regarding (1), in multi-institutional collaborative research, the reporting may be made by the head of the research institution to which the representative investigator is affiliated, by collecting information from all collaborative research institutions. It is also possible that the heads of the research institutions which involved in the serious incompliance, from among the collaborative research institutions, make reporting to

the Minister, respectively. Further, it is also possible to make single reporting by the heads of the research institutions which involved in the serious incompliance, after confirming the contents of the reporting each other.

5 Contents of the "report to the Minister" according to (1) should include descriptions of status and results of necessary measures which have been provided after hearing the opinions of the ethics review committee. As for the ethics review committee to provide opinions, since the ethics review committee that reviewed the pertinent research have knowledge of the contents of the research and the review, it must be the one that reviewed said research.

6 Serious incompliance must be responded "promptly", although the timing of reporting may vary on a case basis. Since the wording is "when he/she has become known ... does not comply with these Guidelines", these Guidelines will not retroactively apply to research which was conducted prior to the effective date of these Guidelines. However, the Ethical Guidelines for Clinical Studies ("Clinical Studies Guidelines") and the Medical Guidelines have the same provision. Thus, if a clinical research is conducted according to the Clinical Studies Guidelines or the Medical Guidelines, the reporting to the Minister of Health, Labour and Welfare may be required according to the Clinical Studies Guidelines or the Medical Guidelines.

7 In (1), the method of making available to the public should be decided taking into account the contents to be made available to the public, but examples can be having a press conference, and posting on the website of the institution that conducts the research.

8 If research conducted abroad is conducted in accordance with these Guidelines based on Section 3-3(1), the requirement of reporting of (1) may apply.

9 In (2), "inspections and investigations" will be conducted when the Minister decides it necessary, in order to confirm the system for conducting research in said research institution, etc.

Section 12 Managing Conflict of Interest (COI)

(1) The investigators shall, when conducting research, appropriately handle situations relating to conflict of interest (COI) of their own regarding the research such as personal income by reporting said situations to the principal investigator for the sake of ensuring transparency.

(2) The principal investigator shall, when conducting research that may be connected with commercial activities such as research relating to validity or safety or pharmaceutical products or medical devices, understand situations of COI relating to the research and describe them in a research protocol.

(3) The investigators shall explain situations of COI described in the research protocol according to (2) to the human research subjects, etc. in the procedures for obtaining informed consent as set forth in Section 8.

1 Section 12 sets forth procedures and responsibilities that must be fulfilled by the investigators and principal investigator regarding COI of the research.
For Guidelines etc. for the understanding of COI, see explanations of Section 7(1).

2 Regarding (1), the investigators are required to report situations relating to COI of their own to the principal investigator based on the institution's internal rules for COI.

3 Regarding (2), the principal investigator is required to understand, besides situations of COI of the research institution reported by the investigators, the research institution's situations of COI of the research in terms of the source of research funding, etc., and describe these in the research protocol.

4 The principal investigator should take account of the institutional system for conducting the research to properly manage COI. Also, to ensure transparency, it is preferable to take appropriate measures such as prescribing a COI management plan specific to the research protocol and a method for checking relationships relating to COI in the research protocol.

5 In an organization that has an institutional COI committee, the head of the research institution should seek opinions of the institutional COI committee for situations of COI being reported by the principal investigator. When seeking opinions of the COI committee, prescribe procedures as institutional rules of the research institution. The institutional COI committee evaluates the situations of COI of the research (may be based on a COI statement, etc.), and when a researcher is found to be in a COI situation, a summary or comment should be reported to the head of the institution and the ethics review committee.

6 In multi-institutional collaborative research, the representative investigator may collect results of review by the COI committees in all research institutions on individual the investigators' COI and submit a single report to the ethics review committee.

Section 13 Storing Samples/Information, etc. for Research

(1) The investigators shall ensure accuracy of information to be used in research and references relating to the information (including records regarding the provision of samples/information to be used in research; hereinafter, "information, etc.").

(2) The principal investigator shall, when storing samples and information, etc., in accordance with the manuals according to (3), describe the method thereof in a research protocol, instruct and manage the investigators such that they ensure accuracy of information, etc., and provide necessary management so that such incident as divulgence, mixing, theft or loss of the samples and the information, etc. can be prevented.

(3) The head of the research institution shall prepare manuals for storing samples and information, etc., and provide necessary supervision such that samples and information, etc. of the research that the head of the research institution has approved to conduct can be stored adequately according to the manuals.

(4) The principal investigator shall report the status of the management according to (2) to the head of the research institution according to the manuals of (3).

(5) The head of the research institution shall, regarding information, etc. which are stored in the research institution, make efforts such that a period of storing can be extended for as long a period as possible, and, when invasive (excluding minor invasion) research involving intervention is conducted, provide necessary supervision such that information, etc. of the research will be stored appropriately at least for a period ending on the day after five years have passed from the date of reporting the completion of the research or the day after three years have passed from the date of reporting the last publication of results of the research, whichever occurs later. The same applies to the storage of pseudonymously processed information and deleted information, etc. (for information relating to a processing method under the provision of Article 41(1) of the APPI, limited to the information which enables restoration of personal information which was used to produce the pseudonymously processed information) and anonymously processed information and information on the processing method, etc. (for deleted information, etc., or processing method information, etc., excluding the case when such information is discarded). In addition, for records regarding the provision of samples/information, the head of the research institution shall supervise necessary to ensure proper storage of the samples/information, for a period of 3 years have passed from the date of the provision when the samples/information are to be provided, or for a period of 5 years have passed from the date on which completion of the research is reported when the samples/information are to be received.

(6) The head of the research institution, when disposing of any of samples and information, etc., shall provide necessary supervision such that they will be provided with adequate measures that will not be able to identify a specific individual.

1 Section 13 sets forth procedures and responsibilities that must be fulfilled by the principal investigator and the head of the research institution regarding the storage of samples/information, etc. In addition, the handling of personal information must comply with rules that apply to personal information handling business operators defined in APPI, administrative organs, etc., and provisions set forth by the local government, besides these Guidelines. For details, see explanations in Section 18.

2 In (1), the term "references relating to the information" encompasses case reports, records prepared by the human research subjects, correction history (including date and name), records regarding the provision of samples/information prepared according to Section 8-3, besides the human subjects' consent forms and the records regarding the provision of samples/information. When making a correction of information, etc., it is preferable to describe the reason why the correction was made, besides correction history (including date and name).

3 In (1), among "information, etc.", the APPI requires to make best efforts to keep personal information of said research accurate and update (address change, etc.), within the extent that is necessary for achieving the purpose of use.

4 In (1), the term "accuracy" encompasses to confirm that information, etc. which are not prepared by the investigators themselves (i.e., records prepared by the human research subjects) have been prepared accurately.

5 Regarding (2), the principal investigator is required to appropriately manage samples and information, etc. and in an organized manner such that they will contribute to the verification of the results of the research. In addition, information, etc. must be stored in such a manner that name of information, etc., place of storage, contents of consent obtained from the human research subjects, etc. can be understood.

6 Regarding the (3), operations of storage of information, etc. may be entrusted to a person designated by the head of the research institution (including appointment of a management officer) or to an outside contractor based on a written agreement including a necessary clause such as security control.

7 Regarding (3), the head of the research institution receives a report on the management status of information, etc. from the principal investigator in accordance with the manuals, and provides appropriate instructions when necessary, and is required to prescribe the manuals to be suitable for the items to be stored while taking also account of the person charged with the storage, place and method of storage, etc.

8 In (3), if the storage uses electromagnetic recording media or the like, in order to adequately store data, the storage must be equipped with a security system and a data backup system, to ensure authenticity, storage stability and readability of the data. Under these conditions, paper media may also be transferred to electronic media for electronic storage.

9 Regarding (5), the heads of the research institution and the principal investigator should take necessary measures for preventing divulgence, etc. or disposal of these information, etc. during the period of mandatory storage, as well as necessary measures for providing the same in response to a request.

10 Regarding (5), since research may need to be verified after years, the heads of the institutions providing existing samples/information as well as research institutions should make best efforts to store information on their provision for as long a period as possible.

11 In (6), examples of taking "adequate measures" can be autoclaving for samples taken from human body, shredding for information fixed on paper media, and deleting data for information stored as electronic data, etc.

Section 14 Monitoring and Audit

(1) The principal investigator shall endeavor to ensure integrity of research, and, when conducting invasive (excluding minor invasion) research involving intervention, conduct monitoring and, as necessary, audit as set forth in the research protocol approved by the head of the research institution for said research.
(2) The principal investigator shall provide necessary guidance and supervision over persons who are engaged in monitoring or audit so that the monitoring and audit will be performed appropriately as set forth in the research protocol approved by the head of the research institution for said research.
(3) The principal investigator shall not allow persons who are engaged in the research that is subject to the audit and persons who are engaged in monitoring thereof to perform audit.
(4) Persons who are engaged in monitoring shall report results of the monitoring to the principal investigator. Also, persons who are engaged in the audit shall report results of the audit to the principal investigator and the head of the research institution.
(5) Persons who are engaged in monitoring or audit shall not divulge information which has become known to them in the course of performing this/her duties, without a justifiable reason. This obligation continues even after they no longer engage in said duties.
(6) The head of the research institution shall cooperate with the conduct of monitoring and/or audit according to (2) and provide measures necessary for such conduct.

1 Section 14 sets forth research subject to monitoring and audit and persons who are engaged in operations thereof.

2 Regarding (1), examples of matters concerning institutional systems and operation procedures to be prescribed in the research protocol for the monitoring and audit can be name of persons who are engaged in monitoring or audit, and, if the operations are to be entrusted, name of the entrustee, etc.
Also, the principal investigator may prepare manuals for monitoring and manuals for audit, and in that case, the research protocol is not required to set forth operation procedures thereof. However, said manuals need to be reviewed by the ethics review committee in accordance with the provision of Section 7(1)(xxv), in the same manner as the research protocol.
As for a determination of necessity of audit, it should be made primarily by the principal investigator in the process of preparing a research protocol, based on a comprehensive assessment of social and academic significance of the research, burdens on human research subjects and expected risks and benefits, etc. for the sake of ensuring quality, transparency, etc. of the research, and be reviewed by the ethics review committee including adequacy of the determination.

3 Regarding (2), instead of applying a uniform method of monitoring, monitoring should be performed appropriately and efficiently taking into consideration the purpose and characteristics of the specific research, etc.
As for a determination of method of monitoring, it may be made, for example, by directly verifying the original references, etc. by a prescribed method, or, in multi-institutional collaborative research, by a method employing EDC (see explanations of Section 8-3), etc. which allows centralized data management and evaluation, etc.

However, such a decision should primarily be made by the principal investigator in the process of preparing a research protocol and the institutional systems and operation procedures need to be described in the research protocol and reviewed by the ethics review committee including adequacy of the decision.

4 Regarding (2), the principal investigator is required to define, besides the method of monitoring, an appropriate scope and method of monitoring in the research such as responsibilities of persons who are engaged in monitoring and items to be evaluated, and prescribe these in the research protocol.

5 Regarding (2), the principal investigator should designate persons who have necessary knowledge, etc. of research ethics and for the conduct of the monitoring or audit as persons who are engaged in monitoring and persons who are engaged in audit.

6 Regarding (3), persons who are engaged in audit may be selected from the personnel of said research institutions, as long as they are other than persons who are engaged in said research or persons who are engaged in monitoring.

7 Regarding (4), results to be reported by persons who are engaged in monitoring include, although they may be changed according to the method of monitoring, date, venue, name of the person charged with the monitoring, items subject to the monitoring, summary of the results of the monitoring, etc.

8 Regarding (4), in multi-institutional collaborative research, persons who are engaged in monitoring and persons who are engaged in audit should share contents of the respective reports with the representative investigator.

9 Regarding (4), results to be reported by persons who are engaged in audit include date, venue, name of the person charged with the audit, items subject to the audit, summary of the results of the audit, etc.

10 Regarding (4), persons who are engaged in audit are required to report the results of the audit to the head of the research institution as well as the principal investigator.

11 Regarding (6), the head of the research institution is required to provide cooperation for persons who are engaged in monitoring or audit for viewing of the information, etc.

Chapter 7 Responses to Serious Adverse Events
Section 15 Responses to Serious Adverse Events

1	Responses of the investigators The investigators shall, when they have come to know that a serious adverse event has occurred in the conduct of invasive research, provide necessary measures according to the procedures or manuals, etc. under subsections 2(1) and 3, such as giving an explanation to the human research subjects, etc., and promptly report it to the principal investigator.

1 Section 15-1 sets forth responsibilities that must be fulfilled by the investigators when a serious adverse event has occurred on the human research subjects in the conduct of research. This provision aims to require reports of all serious adverse events being found in the conduct of research involving invasion, regardless whether or not causation exists between a serious adverse event and said research.

2 "Procedures or manuals, etc." include research protocols and instructions given by the heads of the research institutions as well as the manuals.

3 Preparation of manuals for responses, etc. in case of an adverse event which falls short of the definition of serious adverse event and procedures of reporting by the responder, etc. should be decided at the discretion of each research institution.

4 In research in which a pharmaceutical product or medical device is used, reporting of side effects, etc. when a disease case, etc. which is suspected to be due to an adverse effect or defect of said pharmaceutical product, etc. has been known should be made appropriately taking into consideration the provisions of the Pharmaceuticals and Medical Devices Act.

2 Responses of the principal investigator

(1) The principal investigator shall, when conducting invasive research, prescribe in the research protocol procedures for matters to be performed by the investigators in case of serious adverse event, and provide necessary measures so that responses can be made adequately and smoothly in accordance with the procedures.

(2) The principal investigator shall, in the case where he/she requested a research cooperative institution to obtain samples/information for the research, when a serious adverse event has occurred in any of the research subjects, promptly be reported thereof.

(3) The principal investigator shall, when he/she has come to know that a serious adverse event has occurred in the conduct of invasive research, promptly seek opinions of the ethics review committee on the adverse event, continuation of the research and the like, followed by reporting thereof to the head of the research institution, and, according to the procedures or manuals, etc. under (1) above and subsection 3, respectively, proceed to provide appropriate responses. Also, he/she shall share the information of the occurrence of the adverse event with the investigators who are engaged in the conduct of the research.

(4) The representative investigator shall, when he/she has come to know that a serious adverse event has occurred in the conduct of invasive research being conducted in multi-institutional collaborative research, promptly share the information of the occurrence of the adverse event including the response of (3) with the principal investigator of the collaborative research institution that conducts the research.

(5) When an unpredictable serious adverse event in invasive (excluding minor invasion) research involving intervention has occurred and a direct causation with said research cannot be denied, the principal investigator of the research institution in which the adverse event has occurred shall report thereof to the head of the research institution, and then promptly report thereof to the Minister (limited to the Minister of Health, Labour and Welfare) and make public the status of the responses according to (2) and (3) and results thereof.

1 Section 15-2 sets froth responsibilities that must be fulfilled by the principal investigator when he/she has become aware that a serious adverse event has occurred on the human research subjects.

2 The principal investigator may establish an efficacy/safety evaluation committee, besides the ethics review committee, for deliberation concerning assessment of adverse events and adequacy of continuation of the research associated therewith and modification of the research.

3 The efficacy/safety evaluation committee may be established by the principal investigator, for making recommendations on the continuation, suspension or discontinuation of the research or amendment of a research protocol to the principal investigator by regularly evaluating the progress of the research, safety data and other material evaluation items. To ensure independency of the efficacy/safety evaluation committee from the principal investigator, persons who are engaged in the conduct of the research and the ethics review committee, members of the efficacy/safety evaluation committee should not include a person who is engaged in the conduct of the research, a member of the ethics review committee that reviews

said research or the head of the research institution.

4 The efficacy/safety evaluation committee may evaluate (i) adequacy of continuation of research and (ii) modification of research associated with an assessment of adverse event, etc., among duties that are performed by the ethics review committee, provided that both of the following two criteria are met, and the results of assessment can be replaced with the assessment by the ethics review committee:
- The composition and functions of the efficacy/safety evaluation committee and procedures therefor are properly defiled in the research protocol, and have been reviewed and affirmed by the ethics review committee; and
- Responses are to be made based on the results of assessment by the efficacy/safety evaluation committee, and contents of said assessment including the results thereof are to be reported to the ethics review committee from said efficacy/safety evaluation committee.

5 Regarding (1), the principal investigator is required to request review by the ethics review committee for the prescribed procedures (manual) according to Section 7(1)(xx), same as the procedure for the research protocol. Especially when conducting multi-institutional collaborative research, the representative investigator takes charge of comprehensively performing the procedures for requesting review by the ethics review committee. Thus, how information will be collected from the institutions need to be prescribed in the procedures (manual), as well.

6 Regarding (2), when the system for conducting research include a research cooperative institution, the principal investigator needs to develop the system such that information on the occurrence of a serious adverse event in the research cooperative institution can be promptly shared, so that the principal investigator can know it without delay.

7 Regarding (4), the principal investigator needs to share or report the information that may have adverse effects on the safety of research subjects, have impacts on the conduct of the research, or alter the approval of the ethics review committee on the continuation of the research, with all principal investigators who are involved in the research or to the head of the research institution.

8 Regarding (4), when multi-institutional collaborative research is conducted, the principal investigator of the research institution in which said event has occurred must first report of the occurrence of the serious adverse event to the head of the research institution and then to the representative investigator, but may notify the principal investigators of the other collaborative research institutions via the representative investigator or other person such as a person who is engaged in the clerical procedures (see explanations of Section 11-2(6)). However, said methods of responses need to be prescribed in the research protocol in advance.

9 Regarding (5), the form to be used to make a report to the Minister of Health, Labour and Welfare is as prescribed in Form 3 (the collection of forms at the end of these Guidelines). An example of a method of making available to the public can be posting on the website of the institution conducting the research, etc.

10 If research conducted abroad is conducted in accordance with these Guidelines based on Section 3-3(1), the requirement of reporting of (5) may apply.

3 Responses of the head of the research institution The head of the research institution shall, when invasive research is to be conducted, develop manuals for matters to be performed by the investigators in advance of the research in case of serious adverse event, and provide necessary measures so that responses can be made adequately and smoothly in accordance with the manuals.

1 Section 15-3 sets forth responsibilities that must be fulfilled by the head of the research institution such as prescribing procedures in case of a serious adverse event has occurred on the human research subjects so that the investigators and the head him/herself can take appropriate actions.

2 "Necessary measures so that responses can be made adequately and smoothly in accordance with the manuals" encompass development of institutional systems necessary for adequate and smooth conduct of research.

Chapter 8 Ethics Review Committee
Section 16 Establishment, etc. of Ethics Review Committee

1 Requirements to establish an ethics review committee The establisher of the ethics review committee shall meet all of the requirements given below:
(i) The person is capable of precisely performing the duties relating to the review;
(ii) The person is capable of continuously managing the ethics review committee; and
(iii) The person is capable of impartially and fairly managing the ethics review committee.

1 Section 16-1 sets forth capacities required to the establisher for establishing an ethics review committee.

2 In (i), "capable of precisely performing the duties relating to the review" means having capacities for establishing a secretariat for responding to a request for review made by the principal investigator, etc. and clarifying the contact point thereof, preparing internal rules of the organization and operation of the ethics review committee according to subsection 2(1), and developing an institutional system for smoothly performing clerical works for ethical review while observing these Guidelines.

3 In (ii), "capable of continuously managing the ethics review committee" means having capacities for securing human resources such as a clerical officer necessary for appropriately performing the operations concerning continued steering of the ethics review committee and having a financial basis for convening of regular meetings of the ethics review committee over a long period of time.

4 In (iii), "capable of impartially and fairly managing the ethics review committee" means that the members of the board of Section 17-2(1) are in independent positions and the publication of the ethics review committee according to subsection 2(3) can be made precisely. The establisher of the ethics review committee must check any interests between persons who are involved in the research to be reviewed and the members of the ethics review committee as necessary.

5 The establisher of the ethics review committee may establish more than one ethics review committees only when all of requirements (i) to (iii) are fulfilled.
If the establisher of the ethics review committee suspends or cancels establishment or steering of the ethics review committee for any reason, he/she must immediately contact the principal investigator who requested the review of said ethics review committee so that the review can be taken over by an ethics review committee established by another establisher, and, in addition, the establisher must provide appropriate measures such as providing information of records of cases being reviewed up to that point upon request.

6 The "establisher of the ethics review committee" in the context of these Guidelines is not necessarily a representative of a corporation, academic group or the like, but the head of the organization/facility of a corporation or the like (for example, dean, director of the research center, director of the hospital) may become the "establisher of the ethics review committee" under the condition that the requirements set forth in Section 16-1 are met and the rules of the corporation or the like clearly defines the organization/facility.

2 Responsibilities of the establisher of the ethics review committee

(1) The establisher of the ethics review committee shall develop internal rules for the organization and management of the ethics review committee, and, based on said internal rules, cause members of the ethics review committee and personnel who are engaged in clerical works thereof to perform their duties.

(2) The establisher of the ethics review committee shall appropriately store the references used in the reviewing of research which has been conducted by the ethics review committee for a period ending on the day on which the completion of the research is reported (or for a period ending on the day on which five years have passed from the day on which the completion of the research is reported, if the research is invasive (excluding minor invasion) research involving intervention).

(3) The establisher of the ethics review committee shall, when starting the operation of the ethics review committee, make public the internal rules for the organization and management of the ethics review committee and a list of the members of the board in the Ethics Review Committee Reporting System. Also, the establisher of the ethics review committee shall, at least once per year, make public the history of meetings of the ethics review committee and a summary of the review, in the System; provided, however, that this does not apply to a summary that the ethics review committee finds it necessary to be kept undisclosed for the protection of human rights of human research subjects, etc. and people relevant thereto or rights or interests of the investigators and people relevant thereto.

(4) The establisher of the ethics review committee shall provide measures necessary for ensuring that the members of the ethics review committee and the personnel who are engaged in clerical works thereof will receive education and training regarding the board review and operations related thereto.

(5) The establisher of the ethics review committee shall cooperate with inspections and investigations conducted by the Minister, etc. to make sure that the organization and management of the ethics review committee comply with these Guidelines.

1 Section 16-2 sets forth responsibilities of the establisher such as development of internal rules concerning procedures to be performed continuously from the time of establishing the ethics review committee as the establisher of said ethics review committee and operations of review, and storage of references used in the reviewing of research.

2 Regarding (1), the establisher of the ethics review committee may, besides review of new applications, define patterns of research protocols for which adequate review can be achieved by circulating the research protocol among members instead of convening a meeting, depending on the contents described in a research protocol, and prescribe such patterns in the internal rules.

3 In managing the review, it is also possible to make use of means that allow interactive and smooth communication such as a video conference (excluding voice only means such as telephone). However, the establisher should endeavor to develop the system environment that offers the quality close to the physical attendance to the committee meeting. The chair of the committee is required to give consideration to facilitate the discussion as necessary, so that the attending members can speak up easily, such as by asking each of the attending members if

they have any comments.

4 In (1), when developing "internal rules for the organization and management of the ethics review committee", it is necessary to consider the matters exemplified below and, in order to fulfill the roles, responsibilities, etc. of the ethics review committee, and procedures concerning management of the ethics review committee and storage of references used in the reviewing of research, etc. must be stipulated:
(i) Composition of members, term of office thereof, etc.;
(ii) Method of selecting the chairperson;
(iii) Method of making a decision in case of difficulty in making a unanimous decision;
(iv) Place and method of storing references used in the reviewing of research, etc.; and
(v) Other matters necessary for the management of the ethics review committee.

5 Regarding (3), the history of meetings includes, besides date of review and venue of the meeting, attendance of the members, hours spent for the meetings, etc.

6 In (3), the "Ethical Review Board Reporting System" is published via the website of the Ministry of Health, Labour and Welfare (MHLW): https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html. Those containing contents being determined to be kept undisclosed by the ethics review committee are required to be published by masking or the like such contents in the summary of the review.

7 Regarding (4), the establisher of the ethics review committee must ensure to provide an opportunity of receiving education and training for the review and the operation relevant thereto, in order for the members of the ethics review committee and persons who are engaged in the clerical works thereof to obtaine knowledge necessary for performing review to determine whether or not approval to conduct research can be issued, etc., including knowledge of various rules for research which should be complied with such as ethical guidelines.

Section 17 Roles and Responsibilities, etc. of The Ethics Review Committee

1 Roles and responsibilities

(1) The ethics review committee shall, when requested by the principal investigator to provide opinions as to whether or not conduct of research is qualified for approval, etc., conduct the review including information on conflicts of interest of the research institution and the investigators pertinent to the research in an impartial and fair manner from ethical and scientific viewpoints based on these Guidelines, and provide opinions in writing or by electromagnetic means.

(2) The ethics review committee may, with respect to the research being reviewed according to (1), conduct a necessary inspection or investigation from ethical and scientific viewpoints and provide the principal investigator with opinions such as amendment of the research protocol and suspension of the research and other necessary opinions concerning the research.

(3) The ethics review committee may, with respect to invasive (excluding minor invasion) research involving intervention among the research being reviewed according to (1), provide the principal investigator with opinions concerning research such as amendment of the research protocol; provided that it has conducted an inspection or investigation necessary for ensuring appropriate conduct of the research and reliability of the research results.

(4) Each of the members of the ethics review committee, experts, the personnel who are engaged in clerical works thereof and other relevant personnel shall not divulge information that has been known in the course of performing their duties of the institution, without a justifiable reason. This obligation continues even after he/she no longer involves in said duties.

(5) Each of the members of the ethics review committee and the personnel who are engaged in clerical works thereof shall, when any serious concern arises from the viewpoints of respecting human rights of human research subjects, etc., conducting the research and ensuring impartiality or fairness of review, such as divulgence of information on the research being reviewed according to (1), promptly report such concern to the establisher of the ethics review committee.

(6) The members of the ethics review committee and the personnel who are engaged in clerical works thereof shall receive education and training for obtaining knowledge necessary for conducting review, etc. from ethical and scientific viewpoints, prior to the commencement of the review and relevant works. Also, they shall continuously receive education and training thereafter at an appropriate time.

1 Section 17-1 sets forth responsibilities in review and other operation of the ethics review committee and responsibilities to be fulfilled by members of the ethics review committee and persons who are engaged in clerical works thereof.

2 Regarding (1), when reviewing research protocol for approval of the conduct of research, etc., the ethics review committee is required to consider situations relating to the proper handling of personal information, COI, etc., described in the research protocol. In addition, when a COI review board has been established, it is recommended to promote cooperation between the ethics review committee and said COI review board, such as attaching written opinions of the COI review board, etc. to the documents to be reviewed by the ethics review committee.

3 Regarding (1), the ethics review committee may, depending on the contents of the

research to review, request submission of any other references necessary for the review (such as references on the research institution's systems for conducting research and the investigator's brochure) if there are any such references.

4 Regarding (1), besides "approved" and "declined", examples of other categories of results of review by the ethics review committee can be "deferred", "suspended (further explanation is required to continue the research)", "discontinued (continuation of the research is inadequate)", etc. A category which is unclear about the results such as "approval upon amendment" is not desirable.

5 When conducting the review according to (1) and providing opinions, the ethics review committee needs to submit a record of the meeting showing the process of the review and the attendance of the members at the same time, to the principal (representative) investigator. Of note, especially when conducting a comprehensive review of multi-institutional collaborative research, each actions need to be taken as promptly as possible, since the opinions of the committee will be used as the basis for obtaining approval of the conduct of the research at each research institution.

6 In (2), the ethics review committee may conduct "a necessary inspection or investigation from ethical and scientific viewpoints" on the research that was reviewed by said ethics review committee, in order to ensure protection of human rights of human research subjects and give consideration to welfare, and also, when it has found that an inspection or investigation is necessary to see whether there is a fact that may change the overall assessment of burdens and expected risks and benefits to be incurred by human research subjects.

7 In (3), "an inspection or investigation necessary for ensuring appropriate conduct of the research and reliability of the research results" may be conducted on research which was reviewed by said ethics review committee in the past, when it has found that an inspection or investigation is necessary to see whether there is such a fact that the contents have been fabricated or falsified.

8 Any inspections or investigations according to (2) and (3) conducted by the ethics review committee take place when the ethics review committee finds it necessary, after clearly defining the purpose of the inspection or investigation.

9 In (4), in "experts, the personnel who are engaged in clerical works thereof and other relevant personnel", "other relevant personnel "can be, when people who require special considerations are selected as the research subjects, those who have knowledge on this account and can provide opinions.

10 Regarding (6), contents of education and training should be designed in such a manner that trainees can obtain knowledge necessary for conducting review for approval of the conduct of research, etc., besides various rules for the research which should be generally observed such as ethical guidelines. Examples of methods of education and training include, besides workshops held by the establisher of the ethics review committee, workshops held by other organizations and e-learning, as well.

11 In (6), regarding "continuously receive at an appropriate time", it is recommended to receive education and training at least around once a year.

2 Composition and quorum of meetings, etc.

(1) Composition of the ethics review committee shall meet all of the requirements given below, in order to be able to adequately perform its duties such as reviewing of a research protocol, and a different person shall be appointed for each of the categories (i) to (iii). Also, the same applies to the quorum of meetings:
  (i) It shall have a member whose expertise is in the fields of natural science, including medicine and medical science;
  (ii) It shall have a member whose expertise is in the fields of human/social sciences, including ethics and law;
  (iii) It shall have a member who is capable of providing an opinion from the standpoint of the general public including human research subjects;
  (iv) It shall have more than one member who is not employed by the same institution as that of the establisher of the ethics review committee;
  (v) It shall be composed of both genders; and
  (vi) It shall be composed of at least five members.

(2) The investigators who are engaged in the conduct of research subject to review shall not attend the process of deliberation and decision-making for providing opinions of the ethics review committee. However, they may attend a meeting and provide explanation regarding the research, upon request of the ethics review committee.

(3) The principal investigator who has requested the review shall not attend the process of deliberation and decision-making for providing opinions of the ethics review committee. However, when it is necessary for understanding the contents of the review by the ethics review committee, he/she may attend the meeting upon consent of the ethics review committee.

(4) The ethics review committee may seek expert's opinion, taking account of the object, contents, etc. of the review.

(5) The ethics review committee shall, when reviewing and providing opinions on a research protocol selecting human research subjects who need special considerations, seek opinions of a person who has adequate knowledge about these people, as necessary.

(6) The ethics review committee shall endeavor to make a unanimous decision to provide its opinions.

1 Section 17-2 sets forth a desired composition of the ethics review committee and contents to be reviewed depending on the characteristics of research.

2 Regarding (1), the ethics review committee is expected to form a consensus after having an extensive discussion among members from different standpoints rather than simply appreciating their expertise, in order to obtain fair and well-balanced results of deliberation. It is necessary to clarify who meet (i) to (iv), respectively.

3 Regarding (1), a person may be a member of multiple ethics review committees.

4 In (1)(ii), regarding "a member whose expertise is in the fields of human/social sciences, including ethics and law", examples of expertise in the fields of ethics and law can be persons who are engaged in works of education or research in universities, etc. based on his/her expertise relating to ethics or law, and persons who are engaged in works as a lawyer, judicial scrivener, etc.

5 In (1)(iii), "the standpoint of the general public including human research subjects" means that the person can provide an objective comment from the viewpoint of human research subjects who are not necessary equipped with adequate knowledge on life-sciences and medical research, such as whether explanations described in an informed consent form, etc. reflecting the contents of research can be generally understandable.

6 In (1)(iv), regarding "who is not employed by the same institution as that of the establisher of the ethics review committee" (hereinafter, "external member"), for example, in the case of a university having a university hospital, if the director of the hospital or the director of the medical school is the "establisher of the ethics review committee", the "institution of the establisher of the ethics review committee" is the hospital or the medical school, and a faculty member or other employee of the university who is not assigned to the hospital or the medical school and has no business relationship with these may become an external member.

7 Regarding (2) and (3), since the ethics review committee is an organization established to provide opinions on adequacy of the research to the principal investigator that undertakes said research, it is not appropriate if a person who actually conducts said research or the head of the research institution (including persons who have been delegated with his/her powers or duties) who is in the position of being involved in said research participates in review by the ethics review committee as its member. Therefore, when establishing and steering an ethics review committee, the establisher of the ethics review committee is required to give special considerations for the selection of members and other arrangements such as requesting walkout during deliberation so that the head of the research institution who is in the position of being involved in said research or a person who actually conducts said research will not participate in the review as its member.

8 In (5), for better understanding of those "who need special considerations", see Section 1, "Purposes and Basic Policies", in particular, explanations on basic policies in (vi). Also, when selecting these people as human research subjects, an especially careful consideration must be given.
When the ethics review committee reviews a research protocol describing these people as the human research subject, it is recommended to seek opinions and cooperation of persons who have adequate knowledge of those people and the research, as necessary, before and after the review. In addition, if none of the members is an expert of this field, a written expert opinion may be requested prior to the review.

9 Regarding (6), if it is difficult to reach "a unanimous decision", a vote which is not a unanimous decision may be taken, only if the members tried everything in the deliberation to reach a unanimous decision. Also, even if a decision is made other than by a unanimous decision, a decision voted by a simple majority is not deemed as opinions of the ethics review committee, and it must be voted by a great majority of the attended members. The establisher of the ethics review committee must prescribe requirements that apply to a vote by the members in the internal rules.

3 Expedited review, etc.

(1) The ethics review committee may conduct review by a member who is designated by the ethics review committee (hereinafter, "expedited review") to provide its opinions, if the review falls under any of the categories given below. Results of the expedited review shall be deemed as the opinions of the ethics review committee, and said results of the expedited review shall be reported to all of the members:

(i) When the review is on multi-institutional collaborative research, the entirety of the research has already been reviewed by an ethics review committee according to Section 6-2(5) and opinions that the conduct of the research is adequate have been received;

(ii) The review is concerning minor modifications of a research protocol;

(iii) The review is concerning research that does not involve invasion or intervention; and

(iv) The review is concerning research that involves minor invasion but does not involve intervention.

(2) The ethics review committee may, among the matters of (1)(ii), treat those which are recognized by the committee that confirmation suffices in advance, as matters to be reported, by prescribing specific details and practices relating thereto in the internal rules according to Section 16-2(1).

1 Section 17-3 sets forth expedited review as one of the types of review and cases that can be subject to expedited review. Also, an obligation of reporting of results of expedited review is also stipulated.

2 To conduct expedited review, the establisher of the ethics review committee is required to prescribe scope of application of expedited review and procedures such as a method of review also in the internal rules for the management of ethics review committee according to Section 16-2(1).

3 For expedited review, the ethics review committee may select more than one members and change members according to the field of research subject to review.

4 Members who are charged with expedited review may, when they have determined that it is difficult to review the subject research by expedited review, in view of these Guidelines and the rules prescribed by the establisher of the ethics review committee, request review by the ethics review committee.

5 A member who has received a report of results of expedited review may request the chairperson that the matters being reviewed by the expedited review be reviewed by the ethics review committee again, with a description of the reason for the request. In this case, when finding that the reason is justifiable, the chairperson must promptly convene a meeting of the ethics review committee to review said matters.

6 Regarding (i), the ethics review committee has the same responsibilities regardless of the method of review, whether it is expedited review or ordinary review. To ensure adequate conduct of review, evaluation must be based on necessary information. When expedited review is conducted, the ethics review committee should confirm that it has actually expressed its opinions affirming adequacy of the entire research and how the review was conducted, etc.

7 In (ii), the term "minor modification of a research protocol" means a modification to the extent that does not influence the conduct of the research, which does not increase burdens or risks incurred by the human research subjects. Examples can be change of occupational title of the principal investigator simple re-organization of descriptions of the research protocol such as those necessitated due to typographical errors. The establisher of the ethics review committee is required to prescribe items that may be subject to expedited review in the internal rules for the management of ethics review committee.

8 Regarding (2), among the "minor modifications of a research protocol" of (1)(ii), those which can be designated as matters to be reported need to be specified in the internal rules regarding the management of the ethics review committee which are specified in Section 16-2(1). Examples can be change of the job title of the principal investigator, name change of an investigator, and matters which are apparently not to be reviewed by the committee.

4 Review of research to be conducted by another research institution

(1) When the principal investigator requests an ethics review committee established in a research institution different from his/her research institution to conduct review of research, the ethics review committee shall fully understand the institutional systems relating to the conduct of the research before conducting the review, and provide its opinions.

(2) When an ethics review committee has conducted review of research to be conducted by a different research institution, if said principal investigator further requests review of the same research, it shall conduct said review and provides its opinions.

1 Section 17-4 sets forth responsibilities when the research institution is entrusted to conduct review of research that takes place an external research institution.

2 Regarding (1), when the ethics review committee reviews research that takes place in another research institution, it is required to also consider such matters as institutional systems of the secretariat for research in said research institutions and other institutional systems to be considered necessary for the conduct of research. Also, when the principal investigator requests an ethics review committee which is not established in his/her research institution, it is necessary to make a request after thoroughly understanding the internal rules such as manuals of the ethics review committee to which the review is requested.

3 In (2), Regarding "if said principal investigator further requests review of the same research", examples can be when the ethics review committee has been asked to give opinions on suspension or discontinuation of research such as due to occurrence of a serious adverse event, amendment of a research protocol, etc.

Chapter 9 Basic Responsibilities for Personal Information, etc., Samples and Samples/Information of A Dead Person

Section 18 Protection, etc., of Personal Information, etc.

1 Handling of personal information, etc.
The investigators and the head of the research institution shall, regarding the handling of personal information including security control measures such as prohibition of inadequate acquisition and use of personal information and accuracy ensuring, reporting of divulgence, etc., and responses to disclosure request, comply with rules that apply to personal information handling business operators, administrative organs and the like defined in APPI, and provisions set forth by the local government, besides these Guidelines.

2 Handling of samples
The investigators and the head of the research institution shall, regarding the handling of samples, comply with these Guidelines and also endeavor to provide necessary and appropriate measures according to APPI, provisions of the local government, etc.

3 Handling of samples/information of a dead person
The investigators and the head of the research institution shall endeavor to handle appropriately samples/information from which a specific individual dead person can be identified and provide necessary and appropriate measures in the same way that they handle information relating to a living individual according to APPI, provisions of the local government, etc., besides these Guidelines, in view of the dignity of the dead person and emotional aspects of the bereaved family, etc.

1 Section 18 sets forth the obligation to comply with legal and regulatory provisions that apply to the handling of personal information, and the application of these Guidelines to samples and samples/information from which a specific individual dead person can be identified.

2 Regarding the handling of personal information, etc., of Section 18-1, APPI generally stipulates the following matters:
(i) Rules that apply when obtaining and using personal information;
(ii) Adequate and safe management (data accuracy maintenance, security control measures, supervision of employees and entrustees, etc.);
(iii) Mechanisms for allowing the person's involvement (notification, disclosure, correction of a purpose of use, etc., discontinuation of use, etc.);
(iv) Mechanisms for processing complaints (establishment of an office processing complaints, etc.);
(v) Rules that apply to the generation, use, provision, etc., of pseudonymously/anonymously processed information; and
(vi) Responses in case of an incident of personal information divulgence (Reporting to the PIP Commission, notifying to the person as the provider her/himself of the personal information, etc.)
(vii) Mechanisms for ensuring effectiveness (receipt of reporting, providing advice, recommendation, order, etc. by the PIP Commission).

3 In Section 18-1, as the "rules that apply to administrative organs", when providing administrative organs anonymously processed information, see Chapter 5, Section 5, of APPI, the APPI Guidelines (Administrative organs), the Guidebook on Clerical Responses to APPI (For Administrative Organs) and Q&A regarding APPI (Administrative Organs), etc.

4 The handling of personal information, pseudonymously processed information or

individual-related information in the corporations listed in Appendix 2 of APPI is basically governed by the provisions that apply to the handling of those in the public sector (however, among the provisions of Chapter 5 of APPI, matters relating to personal information files, disclosure, etc., and anonymously processed information are governed by the provisions that apply to administrative organs (see APPI, Article 58(1) and Article 123(2) and (3))). Japan Organization of Occupational Health and Safety (JOHAS) is one of the "administrative organs", but the handling of personal information, pseudonymously processed information or individual-related information in a hospital operated by JOHAS is governed by the provisions relating to the handling of those in the public sector (APPI, Article 58(2) and Article 123(1) and (3)).

5 Under APPI, respecting autonomy of academic research institutions such as the respect of university autonomy, the PIP Commission shall, in light of the spirit of Article 146(1) of APPI (see the Guidelines for the Act on the Protection of Personal Information (Common Provisions)), respect voluntary rules for the proper conduct of research involving the use of personal information which are formulated and published either alone or jointly by an academic research institution, provided that the contents thereof are appropriate from the perspective of protecting individual rights and benefits and the actual handling thereof comply with the voluntary rules. Each of the research institutions being "academic research institutions" is expected to prepare its own rules on the proper handling of personal information, etc., in life-science and medical research involving human subjects as a part of such voluntary rules, referring to the provisions of these Guidelines.

6 In life-sciences and medical research involving human subjects, dead persons may become human research subjects as well as living individuals. Taking into consideration the "Guidance on appropriate handling of personal information in business entities relating to medical services and nursing care" (Notice of Secretary General of the Secretariat of the PIP Commission and MHLW Health Policy Bureau/Pharmaceutical Safety and Environmental Health Bureau/Health and Welfare Bureau for the Elderly, Kojyo No. 534, Isei-Hatsu 0414 No. 6, Yakusei-Hatsu 0414 No. 1, Ro-Hatsu 0414 No. 1 of April 14, 2017) and the "Guidelines for provision, etc. of medical information" (Notice of Director of the Health Policy Bureau of MHLW, Isei-Hatsu No. 0912001 of September 12, 2003) require that security control measures of the same level be provided after the death of patients or users and medical information be provided to the bereaved family, these Guidelines set forth the handling of samples/information of dead persons in Section 18-3.

7 Unless information of a dead person is also information relating to a living individual of kin family or the like, it is not in the scope of application of APPI. However, these Guidelines set forth, while requiring full respect of will and honor of the late person, the scope of the person who may make a request of disclosure and suspension of use of information of a dead person so as to include the spouse, child, farther and mother of the human research subject and persons equivalent to these, in addition to a living individual when information of the dead person is also information relating to said living individual. Procedures for such request are according to APPI, etc.

8 Of note, Section 18-3 applies to the case when a human research subject is passed away after research, or when a dead person was a human research subject. In addition, some information may be information relating to more than one individual, and if information relating to a dead person is also information relating to a living individual concerning kin family of the dead person, it is necessary to respond to the living person as "personal information of a living person" according to Section 18-1.

<References> Legal and regulatory provisions regarding personal information protection

The website (https://www.ppc.go.jp/personalinfo/legal) of the PIP Commission provides links to the following documents:

- Act on the Protection of Personal Information (APPI) (Act no. 57 of May 30, 2003)

- Cabinet Order to Enforce the Act on the Protection of Personal Information (Cabinet Order No. 507 of December 10, 2003)

- Enforcement Rules for the Act on the Protection of Personal Information (PIP Commission Rule No. 3 of October 5, 2016)

- Supplementary rules on the handling of personal data which have been transferred with the adequacy determination from the regions of EU and United Kingdom relating to the protection of personal information (April 2022 by the PIP Commission)

- Guidelines on the Act on the Protection of Personal Information:
  - Common Rules (November 2016 (partially revised on October 2021) by the PIP Commission)
  - Provision to Third Parties in Foreign states (November 2016 (partially revised on October 2021) by the PIP Commission)
  - Obligations of confirming and recording required for third party provision (November 2016 (partially revised on October 2021) by the PIP Commission)
  - Pseudonymously/Anonymously Processed Information (November 2016 (partially revised on October 2021) by the PIP Commission)
  - Accredited Personal Information Protection Organizations (August 2021 (partially revised on October 2021) by the PIP Commission)
  - Administrative Organs (January 2022 by the PIP Commission)

- Q&A for the "Guidelines on the Act on the Protection of Personal Information" (February 16, 2017 by the PIP Commission)

- Q&A regarding the "Guidelines on the Acts on the Protection of Personal Information"

- "Foreign states, etc., having a system on the protection of personal information which is recognized to meet the standard equivalent to that of Japan for the protection of individuals' rights and benefits " (PIP Commission Public Notice No. 1 of 2019)

- the Guidebook on Clerical Responses to APPI (For Administrative Organs) (February 2022 by the Secretariat of the PIP Commission)

- Q&A regarding APPI (Administrative Organs) (February 2022 by the Secretariat of the PIP Commission)

- Pseudonymously/Anonymously Processed Information: For trustful use and utilization of personal information – System - (February 2017 (partially revised on

Marcy 2022) by the PIP Commission)

- Pseudonymously/Anonymously Processed Information: For trustful use and utilization of personal information – Cases - (February 2017 (partially revised on Marcy 2022) by the PIP Commission)

(Form 1)

Date (YYYY/MM/DD): / /

(Application/Report) regarding Provision of Samples/information to An External Research Institution

To: (Name of the head of the provider institution)

Submitted by: Affiliation:
Job title:
Name: seal

We hereby submit a(n) (application/report) on our provision of samples/information retained by us to a(n) (external research institution/collaborative research institution) based on our "Internal rules for the conduct of life-sciences and medical research involving human subjects", with the following details:

Attached references:
☐ Research protocol in the recipient institution
☐ Certificate of ERC approval in the recipient institution
☐ Other ( )

1. Matters relating to research	
Research project	
Research supervisor	Name : Name of the research institution (current affiliation):
Expected research period described in the research protocol	From , 20 to , 20
Items of samples/ information to be provided	Describe to the extent that is necessary to make it possible to understand what samples/information were provided. (e.g., test data, medical records, blood, hair, etc.) Including ☐ samples, ☐ special care-required personal information, ☐ individual-related information, ☐ other.
How the samples/ information were obtained	Describe to the necessary extent to show that the samples/information was acquired by appropriate procedures. (e.g., acquired in the process of medical practice, acquired in the process of conducting xx research, etc.)
Information on the human research subjects ✧ Not required when anonymously processed information or individual-related information is provided, or when the provision is associated with the provision of pseudonymously processed information for joint use.	Describe to make it possible to understand whose samples/information were provided. (e.g., name, research ID)
Method for providing samples/information	
Recipient institution ➢ Including names of collaborative research institution(s) and the principal investigators of the research institutions	Name of the research institution: Job title of the person in charge: Name of the person in charge:

2. Matters that require confirmation	
Obtained consent of research subjects and contents of the consent + Describe to make it possible to understand that informed consent or adequate consent has been obtained for each of the human research subjects, etc.	☐ Informed consent has been received by+ (☐ Writing ☐ Verbally ☐ Electromagnetic record) ☐ Adequate consent has been received.+ ☐ When obtained by simplified informed consent procedure.*1 ☐ When obtained by opt-out*2 (Method of notification, etc. (e.g., by sending a notice, document posting (posting place), website (URL), etc.):) ☐ When the above procedures are not required: ☐ When samples which do not enable identification of a specific individual (limited to the case where the recipient will not acquire personal information) are provided. ☐ When anonymously processed information is provided. ☐ When individual-related information (limited to the case where the recipient is not presumed to acquire the individual-related information as personal information) is provided. ☐ When provided associated with entrustment or joint use.
Method of processing, whether or not deleted information is available	Describe in formation such as whether there is so-called "matrix table", person in charge of management. ☐ Prepared (Managed by:) (Managing office:) ☐ Not prepared
Methods for preparing and storing records regarding the provision of samples/information	☐ This form will be stored as a record. (Managed by:) (Managing office:) ☐ Another form will be sent to the recipient institution, and the recipient institution will store records. ☐ Other ( )

*1 (1) There is a difficulty in obtaining informed consent or adequate consent.
(2) The conduct of research does not involve invasion.
(3) Simplified procedures are not against the interest of the research subjects.
(4) Without simplifying the procedures, the conduct of the research will be made difficult or the value of the research will be considerably undermined.
(5) The research is recognized as socially highly important research.
(6) It is applicable to exceptions prescribed in the items of Article 27(1) of APPI.
(7) An appropriate measure is taken from among the following options:
- PR activities to the population including the research subjects, etc. will be undertaken about the purpose of the collection or use of samples/information, what to be collected, methods to be used, etc.;
- Post-event briefing will be promptly provided to the research subjects, etc.; and
- If samples /information are to be collected or used continuously for a long period of time, efforts will be made to undertake PR activities to inform the society of the actual conduct, including the purpose and method of the collection or use of samples/information, so that the society will be well-informed.

*2 (1) There is a difficulty in obtaining informed consent or adequate consent.
(2) It is applicable to exceptions prescribed in the items of Article 27(1) of APPI.

(*Institutional use for management)	
Review by the ethics review board (ERC)	☐ Not required ☐ Required (Date of approval (YYYY/MM/DD): / /)
Approval of provision (on YYYY/MM/DD)	☐ Approved by the head of the research institution (on / /) ☐ Acknowledged by research cooperative institution (on / /) ☐ Approved by the head of the institution conducting only the provision of existing samples/information (limited to the case of Section 8-1(4)B) (on / /) ☐ Disapproved (on / /)

(Form 2)

Date (YYYY/MM/DD): / /

Report regarding Provision of Samples/information to Another Research Institution

To: Head of the recipient research institution

Provider institution:	Name: Address: Name of the head of the institution: Title of the person in charge: Name of the person in charge:
Recipient research institution:	Name: Name of the principal investigator:

We hereby provide you (as provision to a(n) external institution/collaborative institution) with samples/information to be used in the research, for the research project entitled, "xxxx". Relevant descriptions are as follows:

Descriptions	Details
Items of samples/information to be provided	Describe to the extent necessary to make it possible to understand what samples/information were provided. (e.g., test data, medical records, blood, hair, etc.)
How the samples/information were obtained	Contents of the confirmation that the samples/information were obtained by appropriate procedures (e.g., residual specimens of the samples obtained in the process of medical practice, etc.)
Information on the human research subjects ✧Not required when anonymously processed information or individual-related information is provided, or when the provision is associated with the provision of pseudonymously processed information for joint use.	Describe to make it possible to understand whose samples/information were provided. (e.g., name, research ID)
Whether or not consent has been obtained	☐ Obtained (Method:) ☐ Not obtained
Method of processing, whether or not deleted information is available	☐ Available (Matrix table: ☐ Available ☐Not available) ☐ Not available

* The recipient is required to describe information on the human research subjects separately, when it has acquired the individual-related information as personal information.

End of the document.

(Form 3)

FAX: 03-3503-0595

Report of an unpredictable serious adverse event

Date: _____

To: Minister of Health, Labour and Welfare

We hereby submit a report of an unpredictable serious adverse event relating to the research as described below:

1. Research institution information
   (1) Name of the research institution, and job title and name of the head thereof:
   (2) Name of the principal investigator (PI):
   (3) Title of the research project:
   (4) Research Registration ID No.:
   (*Describe a number, etc. unique to the research for identification, such as an ID number assigned by a research protocol open database to which the research has been registered. Use the same number in all reports of this research by all research institutions involved in the research.)
   (5) Contact person: Phone: FAX:
   e-mail:

2. Descriptions of report
   (1) Institution where the event occurred:
   □The reporting institution □Other institution (Name of institution:)

   (2) Name of the serious adverse event, and any development after the occurrence
   (Provide concise descriptions of date occurred, reason why it is determined serious, contents of invasion or intervention and causation, development, outcome, etc.)

   (3) Measures responding to the serious adverse event
   (Suspension of new registration, revision of informed consent form, re-consent of other human research subjects, etc.)

   (4) Date, summary and results of review by the ethics review committee (ERC), necessary measures, etc.

   (5) Indication that collaborative research institutions have been informed, etc.:
   Any collaborative research institutions : □NONE □YES
   (Total number of institutions (including the reporting institution): ____ institutions)
   Sharing of information with all institutions : □NO □YES
   Method of sharing the information:

   (6) Means of making the results available to the public
   (URL, etc. where the results are or will be available)

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