

(Tentative translation)

Guidelines on clinical research using human stem cells

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Ministry of Health, Labour and Welfare

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Preamble

Clinical research making use of human stem cells (hereunder, “human stem cell clinical research”) is anticipated to play an important role in the maintenance of public health and the prevention, diagnosis and treatment of diseases through the regeneration of organ function and other means.

The “Guidelines on clinical research using human stem cells” (hereunder, the “guidelines”), all involved in human stem cell clinical research should respect, were established in July 2006 to ensure, through respect for the individual and human rights, and the maintenance of scientifically-based safety and efficacy, that the clinically promising field of human stem cell research achieves public understanding and is appropriately implemented and maintained.

In the following years, advances have been made in clinical development of stem cells known at the time, and new types of stem cells, such as induced pluripotent stem cells (iPSCs) and human embryonic stem cells (ESCs), which are also now the subject of intensive fundamental research geared toward clinical application, leading to a high level of expectation for their potential use in the treatment of fatal or highly debilitating medical conditions. Research systems also continue to diversify. Clinical research will be essential in order for the fruits of stem cell research currently underway to become established as treatments for a wide range of conditions.

Given the present situation, the guidelines have been amended to include human iPSCs (hiPSCs) and human ESCs (hESCs) within their scope, and to further promote research and development. Moreover, the diverse research systems have been clarified so as to afford stronger protections for the safety and ethical treatment of clinical research subjects and donors (hereunder, “research subjects and donors.”).

Much remains unknown about the effects on the human body of human stem cell clinical research in general, and hiPSCs and hESCs in particular, and consequently such research must be carried out at institutions which have established robust systems for the protection of the safety and ethical interests of research subjects and donors. In addition, to avoid confusing people by biased information causing either unrealistic hopes of immediate treatment applications or exaggerated concerns, institutions conducting clinical research are expected to actively disseminate information regarding their work so as to allow for the acquisition of scientifically based knowledge.

Looking forward, these guidelines may need to be amended in light of future technological

developments or scientific findings. At such times, the Ministry of Health, Labor, and Welfare (MHLW) will convene a committee of experts in medicine and bioethics to review amendments in an objective and comprehensive manner. Finally, the MHLW committee shall review all human stem cell clinical research on an individual basis in light not only of these guidelines, but of the latest scientific findings.

Chapter 1 General rules

Paragraph 1 Objectives

Human stem cell clinical research is anticipated to play an important role in the maintenance of public health and the prevention, diagnosis and disease through the regeneration of organ function and other means.

In light of this role, these guidelines set forth points to be observed by all persons involved in human stem cell clinical research with the objective of achieving public understanding, and the appropriate implementation and advancement of such research through respect for the individual and human rights and the maintenance of scientifically-based safety and efficacy.

Paragraph 2 Definitions

In these guidelines, the following terms shall be defined as follows.

- (1) “Human stem cells” are human cells capable of self-renewal (the ability to generate of progeny cells of identical capacity through replication; also below) and differentiation (the ability to give rise to cells of other lineages; also below), and include human somatic stem cells, hESCs and hiPSCs, as defined in the detailed regulations (hereunder, “details”) set forth by the MHLW Health Section director.

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- 1 Human somatic stem cells are stem cells that are present in the human body that possess limited differentiative potential. These include hematopoietic stem cells (capable of differentiation into all types of blood cells), neural stem cells (capable of differentiation into neurons and other neural cell types, such as glia), and mesenchymal stem cells (capable of differentiation into cell types including bone, cartilage and fat cells). These guidelines also cover clinical research involving the use of tissues that contain somatic stem cells, such as bone marrow and umbilical cord blood.
- 2 Human embryonic stem cells are cells obtained from the inner cell mass of blastocysts derived from fertilized human oocytes and grown in culture, which are in an undifferentiated state and have the capacity for both self-renewal and pluripotent differentiation.
- 3 Human induced pluripotent stem cells are stem cells generated by the artificial induction of pluripotency, which exhibit properties highly similar to those of human embryonic stem cells. Cells which have been directly reprogrammed to cell types of limited differentiative potential (for example, the generation of neural stem cells from skin fibroblasts without first reverting to a

pluripotent iPSC state), while they cannot be considered iPSCs, also fall within the scope of these guidelines.

- (2) “Researchers” are persons engaged in human stem cell clinical research; this term excludes principal investigators.
- (3) “Principal investigators” provide necessary instructions to researchers engaged in human stem cell clinical research, and oversee work responsibilities relating to such research.
- (4) “Study leaders” provide necessary instructions to researchers and principal investigators engaged in human stem cell clinical research involving tissue collection, processing and transplantation or administration that is carried out at multiple institutions, and oversee work responsibilities relating to such research. Study leaders must be appointed from among the study’s principal investigators.
- (5) “Researchers, etc.” refers to all persons engaged in a human stem cell clinical research study, including researchers, principal investigators, and institute directors.
- (6) “Research institution” refers to the institution at which human stem cells (or human cells differentiated from human stem cells) for use in human stem cell clinical research are collected or processed.
- (7) An “ethics review committee” reviews items necessary to the implementation, continuation or alteration of a human stem cell clinical research plan from ethical and scientific perspectives, and serves as an advisory body to the institute director at the institution at which the human stem cell research takes place.
- (8) “Serious situations” are occurrences of the death of a research subject or other serious developments during the conduct of human stem cell clinical research, or the receipt of information that may be thought to have an impact on the implementation of such research.
- (9) “Research subjects” are persons who are subject to transplantation or administration during the course of human stem cell clinical research.
- (10) “Donors” are persons who provide their own human stem cells or differentiated cells during the course of human stem cell clinical research.
- (11) “Informed consent” refers to the process in which the principal investigator, or a researcher working under instructions from the principal investigator, of a human stem cell clinical research study provides an explanation regarding the study in advance, such that research subjects, donors, or their proxies, gain an understanding of the significance, aims, and methodology of the study, and freely provide consent the principal investigator, or a researcher working under instructions from the principal investigator

with regards to becoming a research subject or donor in the study, and to the handling of human stem cells, etc. as set forth in section 5, above.

- (12) “Proxies” are persons capable of providing informed consent on behalf of other person who may serve as research subjects or donors, but who lack autonomous competency to provide consent, such as those with parental rights, spouses, heirs, and others judged capable of representing their intents and best interests.
- (13) “Processing” refers to the manipulation of human stem cells, such as minimal manipulation, artificially induced proliferation, drug treatments intended to activate cells or elicit other effects, modification of biological properties, combination with non-cellular components, or genetic engineering.

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Minimal manipulation refers to manipulation of cells in ways that do not affect their inherent biological properties, such as tissue isolation, tissue sectioning, isolation of human stem cells or differentiated cells, treatment with antibiotics, washing, sterilization by gamma rays or other means, freezing, and thawing.

- (14) “Processing institution” refers to the institution at which human stem cells to be used in the human stem cell clinical research are processed.
- (15) “Lot” refers to a single homogeneous population of human stem cells processed using the same processing methods.
- (16) “Final preparation” refers to the processed human stem cells or other product to be transplanted or administered to research subjects.
- (17) “Personal information” refers to information relating to living persons, including identifying information such as name and date of birth that might be used to distinguish individuals (including information that might be used to identify individuals easily). In cases in which the information relating to a deceased person is simultaneously information about that person's surviving relatives, it shall be treated as information relating to the surviving individual.
- (18) “Stored personal information” refers to personal information obtained by researchers, etc. during the course of human stem cell clinical research for which said researchers, etc. have the right to disclose, amend, add or delete, terminate usage, erase, or stop the provision to third parties thereof.
- (19) “Underage persons” are persons below the age of 20 years who have never married.
- (20) “Surrogates” are legal representatives of minors or adult wards assigned by the individual with requesting notification of usage objectives, disclosure, amendment, addition or deletion, termination of use, or stoppage of provision to their parties (hereunder, “request for disclosure, etc.”) of personal information.

Paragraph 3 Scope

1 The present guidelines cover human stem cell clinical research intended to study the transplantation or administration of human stem cells, etc. into the human body for the treatment of medical conditions outlined in Chapter 4.

However, the following cases are not covered under these guidelines.

- (1) General medical practices of established safety and efficacy.
- (2) Clinical trials conducted under the Pharmaceutical Affairs Law (1960 Law 145)

2 These guidelines cover human stem cell clinical research conducted domestically within Japan, but in cases in which a Japanese research institution engages in human stem cell clinical research in another country, the researchers, etc. are required to comply basic standards sets forth in these guidelines while remaining in compliance with the laws and guidelines of the country in which the research is conducted.

However, in cases in which the laws and guidelines of the country in which the human stem cell clinical research is conducted are stricter than those set forth in the present guidelines, such research must be conducted in compliance with such standards.

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In cases in which a Japanese research institution conducts research outside of Japan, or in collaboration with a foreign research institution, in cases in which the standards of the country in which the research is conducted are stricter than those set forth in the present guidelines, and the following criteria are met, the research may be conducted following the standards of the other country.

- (1) It would be difficult to comply with these guidelines in the other country.
- (2) The following measures are in place in deemed appropriate by the institute director following review by the Japanese ethics committee.
 - 1) Informed consent can be obtained.
 - 2) Appropriate measures are in place for the protection of research subject and donor personal information.
 - 3) The research plan is acceptable from the other country's ethical and scientific perspectives, approved by ethics committee or equivalent body in accordance with the laws of the other country, and approved by the director of the research institute in the other country.

Paragraph 4 Medical conditions

1 Human stem cell clinical research is aimed at the regeneration of organs or tissues lost or damaged due to injury or disease.

- 2 First-in-human studies of human stem cells in transplantation or administration (hereunder, “novel human stem cells”) must meet all of the following criteria.
 - (1) Studied for the treatment of a medical condition that is life-threatening, severely debilitating, or disfiguring to the degree that it results in a significant reduction in quality of life.
 - (2) The treatment efficacy of the human stem cell clinical research is predicted to significantly surpass that of currently available treatments.
 - (3) The benefits of the human stem cell clinical research to research subjects are strongly predicted to outweigh the risks.

Paragraph 5 Human stem cells

- 1 The following types of cells shall be considered as human stem cells for use in transplantation or administration to research subjects in human stem cell clinical research.
 - (1) Human stem cells and tissues enriched for such cell populations
 - (2) Cells or tissues obtained by processing (1)

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Human embryonic stem cells shall not be used in clinical research until standards have been established for the clinical research use of human embryos.

- (3) Cells or tissues obtained by processing human stem or differentiated cells (excluding cells obtained solely by minimal manipulation)
- 2 Stem cells collected from human fetuses (including dead fetuses) are not covered under these guidelines.

Paragraph 6 Basic principles

- 1 **Maintaining ethicality**

Researchers, etc. must act with respect for ethical considerations
- 2 **Maintaining safety and efficacy**

Human stem cell clinical research must be limited to experiments that are predicted on the basis of scientific knowledge to be safe and efficacious
- 3 **Quality control**

Human stem cells used in human stem cell clinical research must be of confirmed quality, safety and efficacy

4 Informed consent

Informed consent must be obtained from prospective research subjects and donors (including proxies, as set forth in Chapter 2, Section 1)) in human stem cell clinical research. Additionally, the person obtaining the informed consent (hereunder, the “person providing explanation”) must be the principal investigator or working under the instructions of the principal investigator, and in principle, must be a physician.

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The definition of physician described in 4 includes dentists.

5 Public health considerations

Human stem cell clinical research must be conducted with due consideration for public health safety.

6 Public access to information

Human stem cell clinical research studies must be registered in a database as set forth in Chapter 2 Section 1.3.(8), and made public in an adequate and accurate manner.

7 Protection of personal information

- (1) Personal information linked to research subjects and donors shall be anonymized (when necessary, the information should be labeled with an identifying code to make it possible to distinguish between individuals). Note that research institutions must be aware of the requirement to handle personal information in compliance with relevant laws and regulations as set forth variously in The Personal Information Protection Act (Act No. 57, 2003), Law on the Protection of Personal Information Held by Administrative Organs (Act No. 58, 2003), and the Law on the Protection of Personal Information Held by Independent Administrative Institutions (Act No. 59, 2003) as well as provisions for the protection of personal information by local governments set forth in Article 11 Paragraph 1.
- (2) Researchers, etc. and ethics committee members involved in human stem cell clinical research must not leak personal information obtained during the course of, or after the end of their involvement in, such research.

Chapter 2 Research systems, etc.

Paragraph 1 Research systems

1 Basic responsibilities for all researchers, etc.

- (1) The life, health, privacy and dignity of research subjects and donors is the responsibility of all researchers, etc. engaged in human stem cell clinical research.
- (2) Researchers, etc. must conduct human stem cell clinical research only in accordance with commonly accepted scientific principles, and based on information from published scientific articles and experimental results. In principle, human stem cells used in transplantation or administration into humans should be predicted to show efficacy based on animal studies, and consideration must be given to the extent possible to their mechanism of action. Additionally, special consideration must be given for the safety (including tumorigenicity) of human stem cells used in human stem cell clinical research.

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Special consideration for safety as described in (2), above, may include the following and should make efforts to reflect any advances in technology.

- (1) Preventing contamination by cells other than the human stem cells predicted to show efficacy.
 - (2) Evaluation methods (such as genomic, epigenetic tests) appropriate for the specific properties of the cells to be transplanted or administered to research subjects.
 - (3) In cases in which tumorigenicity is considered a risk, exclusion of the risk by appropriate animal studies is desirable.
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- (3) Person providing explanations must give full explanations of all necessary information to prospective research subjects and donors regarding the human stem cell clinical research, and obtain informed consent in writing.

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- 1 Informed consent must be obtained for each case of collection, transplantation or administration.
 - 2 Separate written informed consent does not need to be obtained by each person providing explanation, but may, for example, be obtained by the principal investigator acting as a representative who obtains written informed consent from each research subject and donor.
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- (4) When conducting human stem cell clinical research that poses a risk of environmental impact, or which involves the use of animals, researchers, etc. must show due consideration for the environment and research subjects and donors.
 - (5) When conducting human stem cell clinical research using novel human stem cells,

researchers, etc. must seek verification from researchers in other disciplines, and show give consideration to the opinions of patient organizations, etc.

- (6) Researchers, etc. have the following responsibilities with respect to the protection of personal information.
 - 1) Take care to prevent the identification of research subjects and donors when publishing the results of the human stem cell clinical research.
 - 2) Make use of held personal information for purposes beyond the scope of the usage objectives for which informed consent has been obtained without prior consent from research subjects and donors.
 - 3) In cases in which the usage objective for stored personal is changed (excluding cases described in 4)), the nature of the changes must be explained to research subjects and donors, and their consent obtained. However, this excludes cases set forth in the detailed regulations.

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The cases described in 3) above are as follows.

- (1) Cases as prescribed by law.
- (2) Cases in which it would be difficult to obtain the individual's consent and in which it is deemed necessary to protect human life, safety or property.
- (3) Cases in which it would be difficult to obtain the individual's consent and in which it is deemed necessary for the improvement of public health or the promotion of child welfare.
- (4) Cases deemed necessary for administrative duties carried out under the law by national or local government institutions or their assignees for which the obtaining of informed consent from the individual may pose a risk of interfering with such duties.
- 4) Research subjects and donors must be informed or notified of the nature of changes to the usage objectives for held personal information in cases in which such changes are reasonably deemed to be relevant to the previous usage objectives.
- 5) When other researchers, etc. receive held personal information for the purpose of continuing the research, they must not handle such personal information in ways that exceed the scope of the usage objectives without first obtaining consent from research subjects and donors.
- 6) Personal information must not be obtained through deception or other improper means.
- 7) Efforts must be made to maintain personal information in an accurate and up to date manner within the scope necessary to fulfill the research objectives.
- 8) Appropriate measures must be taken for the safe keeping of held personal information

so as to prevent its leakage, loss or damage.

Moreover, information relating to deceased persons shall be handled with the same care as held personal information so as to maintain the dignity of the deceased and out of consideration for the feelings of their survivors, and appropriate measures must be taken for the safe keeping of such information so as to prevent its leakage, loss or damage.

- 9) Held personal information must not be provided to third parties without obtaining the prior consent of research subjects and donors. However, this excludes cases set forth in the detailed regulations as follows.

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- 1 The exceptions described in 9) include the following.
 - (1) Cases as prescribed by law.
 - (2) Cases in which it would be difficult to obtain the individual's consent and in which it is deemed necessary to protect human life, safety or property.
 - (3) Cases in which it would be difficult to obtain the individual's consent and in which it is deemed necessary for the improvement of public health or the promotion of child welfare.
 - (4) Cases deemed necessary for administrative duties carried out under the law by national or local government institutions or their assignees for which the obtaining of informed consent from the individual may pose a risk of interfering with such duties.
- 2 In the following cases, the transfer of held personal information to third parties as described in 9) does not apply.
 - (1) Cases in which all or part of the held personal information kept by researchers, etc. is assigned to a third party as needed within the scope of the usage objectives.
 - (2) For cases in which use of the held personal information is shared with specific persons, in which the research subjects and donors have been notified in advance or provided with ready access to the items of stored personal information, the extent of the users with whom such information is shared, the names of those responsible for the shared use and the objectives for which they will use the shared information. Moreover, research subjects and donors must be notified in advance by the researchers, etc. in the event of changes to the research objective or the names of persons responsible for the handling of stored personal information.
- 10) Complaints and inquiries by research subjects and donors regarding the handling of held personal information must be responded to rapidly.

2 Responsibilities of researchers

- (1) Researchers engaged in human stem cell clinical research must have the necessary specialized knowledge and clinical experience to properly conduct such research.

- (2) Researchers engaged in human stem cell clinical research must receive the education and training, and work to gather information, needed to properly conduct such research.
- (3) Researchers must support the principal investigator in creating materials relating to the human stem cell clinical research plan, and report to the principal investigator as necessary to the conduct of such research.

3 Responsibilities of principal investigators

- (1) One principal investigator meeting the following requirements shall be assigned for each research institution engaged in human stem cell clinical research.
 - 1) The principal investigator must have sufficient scientific knowledge and medical experience and knowledge of the medical condition that is the subject of the human stem cell clinical research and related fields.

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In the event that the principal investigator does not have sufficient medical experience or knowledge, a physician with sufficient clinical experience must participate in the human stem cell clinical research.

- 2) The principal investigator must have sufficient ethical perspective needed to conduct human stem cell clinical research.
- (2) The principal investigator must give consideration to the scientific and ethical basis of the human stem cell clinical research using information gathered from sources internal and external to the study.
- (3) The principal investigator must predict risks of the human stem cell clinical research, and must not conduct such research in cases when safety cannot be sufficiently ensured.

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The principal investigator must collect information needed to predict risks and ensure safety until the end of the human stem cell clinical research, and must put in place measures for observation and response.

- (4) The principal investigator must not appoint researchers, etc. on economic grounds.
- (5) On the implementation, continuation or alteration of human stem cell clinical research, the principal investigator must prepare documents (hereunder, “research plans”) that outline systems necessary to the conduct of the research following due consideration for (2), above, and receive the approval of the research institute director.

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- 1 Continuation of human stem cell clinical research as set forth in (5), above, includes both the continuation of such research beyond its implementation period, and the restarting of human stem cell clinical research that was previously stopped for any reason.
- 2 The research institute director set forth in (5), above, may be construed as following.
 - (1) In cases in which the research institution is a hospital, the hospital director
 - (2) In cases in which the research institution is a university medical school, the head of the medical school
- (6) The principal investigator must include the following items in the research plan.
 - 1) The name of the human stem cell clinical research
 - 2) The names of the principal investigator and researchers and their roles in the human stem cell clinical research
 - 3) The name and address of the research institution
 - 4) The objective and significance of the human stem cell clinical research
 - 5) The medical condition and reason for its selection
 - 6) Criteria for the selection of research subjects
 - 7) The types, and methods of collection, processing, and transplantation or administration of the human stem cells
 - 8) Evaluation of safety
 - 9) Reasons for why the human stem cell clinical research is considered feasible
 - 10) Plan for the implementation of the human stem cell clinical research
 - 11) Procedure for obtaining informed consent from research subjects and donors
 - 12) Items to be explained in obtaining informed consent
 - 13) In cases in which the human stem cell clinical research involves human subjects for which it may be difficult to obtain consent directly from the individual, justifications for why such research is necessary, and criteria for the selection of proxies
 - 14) Procedures for the handling of serious situations
 - 15) Method of follow-up study after the completion of the human stem cell clinical research
 - 16) Provisions necessary for compensating research subjects who may suffer damaged health in the course of the human stem cell clinical research
 - 17) Methods for the protection of personal information (including methods for anonymization in a linkable fashion)
 - 18) Other necessary items

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Other necessary items as described in 18) may include the following.

- (1) Method of procurement of research funds for the human stem cell clinical research
 - (2) Items showing originality in comparison to existing human stem cell clinical research
- (7) The following materials must be attached to the research plan described in (6), above.
- 1) Curricula vitae and research achievements for the principal investigator and researchers
 - 2) Overview of the facilities at research institution as described in 7
 - 3) Research results relating to the quality, etc. of the human stem cells to be used in the human stem cell clinical research
 - 4) Overview of the internal and external research relating to said human stem cells
 - 5) Plain language summary, to the extent possible, of the human stem cell clinical research
 - 6) Format of the explanation and consent forms to be used in the informed consent process
 - 7) Other necessary materials
- (8) The principal investigator must register the research plan for the human stem cell clinical research in advance in a publicly accessible database (limited to those maintained by the National University Council of Japan, The Japan Pharmaceutical Information Center, and the Japan Medical Association). However, in cases in which this would result in difficulties due to problems of intellectual property, etc., this may be waived with the acknowledgment of the ethics committee and the approval of the institute director.

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- 1 There may be cases in which the institute director makes the registration, but in such cases, the responsibility for registering continues to lie with the principal investigator.
 - 2 In cases in which human stem cell clinical research is conducted in collaboration with other research institutions, the principal investigator from one institution may act as a representative for the others and register the information a single time. In such cases, information relating to all participating research institutions must be included in the registration.
- (9) The principal investigator must oversee the human stem cell clinical research, providing necessary instruction to other researchers, and conduct ongoing education and training.

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Training as described in (9), above, may include training with regard to the following.

- (1) Understanding of the present guidelines.

- (2) Knowledge of human stem cells (including the ethical handling of human stem cells)
 - (3) Knowledge and techniques for the handling of processed human stem cells
 - (4) Knowledge and techniques relating to facilities and equipment
 - (5) Knowledge and techniques relating to safety in processes used in processing
 - (6) Knowledge and techniques relating to response to accidents
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- (10) The principal investigator must follow the research plan for the human stem cell clinical research and continuously ensure its proper implementation.
 - (11) The principal investigator must submit occasional reports on the human stem cell clinical research progress to the institute director on a regular basis at least once per year.
 - (12) In the event of a serious situation, the principal investigator must rapidly submit reports to that effect to the institute director and the study leader. The principal investigator may, as necessary, suspend such clinical research or take other provisional actions prior to receiving instructions from the institute director and the study leader.
 - (13) In the event that the anticipated benefits of the human stem cell clinical research are determined to be outweighed by the burdens, the principal investigator must terminate said clinical research. Moreover, human stem cell clinical research must be terminated once it has produced sufficient results.

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- 1 Until the termination of the human stem cell clinical research, the principal investigator should monitor information reported at foreign and domestic scientific meetings and in the published literature (hereunder, “published information”) and report it to the institute director.
 - 2 In cases of collaboration with other research institutions, the principal investigator should report published information he/she has obtained to researchers, etc. at the collaborating research institution(s).
 - 3 In the event that the human stem cell clinical research is suspended or terminated, the principal investigator must submit a report to that effect to the institute director.
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- (14) The principal investigator must takes such measures as necessary, and make a report to that effect, upon receiving instructions from the institute director or study leader.
 - (15) In the event that the human stem cell clinical research is suspended or terminated, the principal investigator must prepare a comprehensive report and submit it to the institute director and study leader.
 - (16) The principal investigator must include the following items in the comprehensive report.

- 1) Name of the human stem cell clinical research
- 2) The objective and term of the human stem cell clinical research
- 3) Names of the principal investigator and researchers
- 4) Name and address of the research institution
- 5) The research plan of the human stem cell clinical research
- 6) The results and implications of the human stem cell clinical research
- 7) The method of follow-up study after the completion of the human stem cell clinical research
- 8) Other necessary items

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Other necessary items described in 8), above, may include such items as methods for dealing with serious situations.

- (17) The principal investigator must conduct follow-up studies of efficacy and side effects for an appropriate period after the completion of the human stem cell clinical research as necessary to ensuring safety and efficacy. The results of such studies must be reported to the institute director and study leader.

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In cases in which there is a risk of tumorigenic activity by transplanted or administered human stem cells, long-term follow-up is desirable.

- (18) Following the end of the human stem cell clinical research, the principal investigator must work to ensure that research subjects receive the best possible preventative, diagnostic and treatment care.
- (19) The principal investigator must maintain records relating to the human stem cell clinical research in good condition for at least 10 years following the submission of the comprehensive report.
- (20) The principal investigator has the following responsibilities with regard to the protection of personal information.
 - 1) Provide necessary and appropriate oversight of the handling of held personal information by researchers so as to ensure the safety of said information.

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The principal investigator must cooperate in efforts by the institute director to develop systems and procedures for the rigorous administration of stored personal information.

- 2) In cases in which all or part of the held personal information is assigned, provide necessary and appropriate oversight of the handling of held personal information by assignees so as to ensure the safety of said information.

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The necessary and appropriate oversight described in 2), above, may include such actions as clearly designating the safety measures with respect to held personal information to be taken by assignees, and confirming its strict compliance.

- 3) The following items of information must be made available to research subjects and donors (must be provided without delay upon request by research subjects and donors).
 - 1 The names of researchers and research groups involved in the human stem cell clinical research.
 - 2 The usage objectives for all held personal information. However, this excludes the following.

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The following cases are excluded from the requirements in 3) 2 above.

- (1) Cases in which there is a risk that the notification or publication of the usage objective would result in damage to the life, health, property or other interests of the research subject or a third party.
 - (2) Cases in which there is a risk that the notification or publication of the usage objective would result in damage to the rights or best interests of research subject or a third party.
 - (3) Cases deemed necessary for administrative duties carried out under the law by national or local government institutions or their assignees for which the obtaining of informed consent from the individual may pose a risk of interfering with such duties.
 - (4) Cases in which the usage objective is considered clear given the circumstances of the acquisition
- 3 Procedures for handling requests for disclosure
 - 4 Contact information for complaints and inquiries
- 4) Upon request by a research subject or donor, or the surrogate thereof, for the disclosure of held personal information usable to identify said research subject or donor, the delivery of written disclosure of such information must be made to the a research subject or donor, or the surrogate thereof, without delay, following the agreed upon method.

In the event that no identifying information exists, the research subject or donor must be informed to that effect.

However, in the event of the following, the disclosure of all or part of said information may be withheld.

- 1 Cases that involve the risk of damage to the life, health, property or other interests of the research subject or a third party.
- 2 Cases in which such disclosure would present a significant difficulty to the appropriate conduct of the human stem cell clinical research.
- 3 Cases that would violate other laws.

In the event that a decision is made not to disclose all or part of information for which disclosure has been requested, the research subject or donor, or the surrogate thereof, must be notified to that effect without delay. Efforts should be made at that time to explain the reasons for such decision to the research subject or donor, or the surrogate thereof.

Moreover, in cases in which other laws govern the disclosure of personal information, the provisions of said laws shall hold force.

- 5) In cases in which held personal information to be disclosed includes medical information, the provisions of the “Guidelines on the provision of medical information” (issued by the MHLW Health Policy Bureau on September 12, 2003, No. 0912001) shall hold force.
- 6) In cases in which a research subject or donor, or surrogate thereof, requests amendment, addition, or deletion of content, stoppage of use, erasure or stoppage of the provision to third parties of held personal information (hereunder, “content amendment, etc.”), after determining its appropriateness, the requested action must be taken.

However, in cases in which the stoppage of use or erasure would be difficult due to involving great expense, etc., alternative measures may be taken as needed to protect the research subject’s or donor’s rights and interests.

- 7) In cases of requests for content amendment, etc., the research subject or donor, or the surrogate thereof, must be notified without delay of the decision to take the requested action, take no action, or take alternative measures, and efforts should be made to explain the reasons for such decision.
- 8) Research subjects or donors, or surrogates thereof, may request that information be provided to enable the identification of held personal information. In such cases, measures should be in place to allow for the simple and accurate making of requests for the disclosure of such information by research subjects or donors, or surrogates thereof, out of consideration for their convenience.

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The principal investigator must make efforts to put measures in place for centralized responses to disclosure requests so as to minimize the burden on research subjects or donors, or surrogates thereof.

- (21) The principal investigator must put measures in place as required to perform oversight of items (2) through (20), above.
- (22) In human stem cell clinical research in which collection, processing and transplantation or administration take place at different institutions under the supervision of a study leader, other principal investigators may request the study leader to register said research as described in (8), above.

4 Responsibilities of study leaders

- (1) In cases in which collection, processing and transplantation or administration take place at different institutions, one study leader shall be appointed for each human stem cell clinical research study.
- (2) The study leader may perform all the duties of a principal investigator, as well as be requested by other principal investigators to register the human stem cell clinical research study in a public database, as described in 3(8), above.
- (3) On the implementation, continuation or alteration of the human stem cell clinical research, the study leader must prepare research plans as described in 3(5), above, and receive the approval of the research institute director.
- (4) The study leader must provide oversight of the human stem cell clinical research and provide instruction as necessary to other researchers, etc., as well as appropriate education and training.
- (5) In the event of a serious situation, the study leader must rapidly submit a report to that effect to the institute director. The study leader may, as necessary, suspend such clinical research or take other provisional actions prior to receiving instructions from the institute director.
- (6) The principal investigator must put other measures in place as required to perform oversight of the human stem cell clinical research.

5 Responsibilities of institute directors

- (1) Ethical awareness
The institute director must thoroughly cultivate awareness of the respect for individual dignity and human rights of research subjects and donors on the part of all researchers, etc. (except the institute director) engaged in human stem cell clinical research, so as to avoid giving rise to ethical, legal, or social problems.

(2) Establishment of ethics committee

The institute director at an institution at which human stem cell clinical research is to take place must establish an ethics committee charged with evaluating the appropriateness of items in the research plan from ethics and scientific perspectives.

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In cases in which a similar committee already exists at an institution, the ethics committee, as set forth in (2), may be reincorporated in a manner to allow it to comply with the requirements for an ethics committee under these guidelines, regardless of the committee's name.

(3) Approval of the implementation of human stem cell clinical research

As set forth in 3(5) and 4(3), on receiving an application to implement human stem cell clinical research, or a significant change to an implementation, as in the details below, the institute director must, after seeking opinions from the ethics committee, and subsequently the Minister of Health, Labor and Welfare, render a decision whether or not to approve said implementation and at the same time indicate any items necessary to said clinical research. In the event that the institute director receives a negative opinion from either the ethics committee or Minister of Health, Labor and Welfare, he/she may not approve the implementation of said clinical research.

For research plans in which the ethics committee or Minister of Health, Labor and Welfare has indicated points of concern or in need of amendment, in the event that the institute director receives an amended or amended version of the research plan from the principal investigator, he/she must inform and the seek the opinion of the ethics committee or Minister of Health, Labor and Welfare regarding the changes, and render a decision whether or not to approve said implementation.

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Significant changes to the implementation as set forth in (3) may include changes to such items as the target medical condition, the type of cell or collection method to be used, or the processing or method of transplantation or administration in the human stem cell clinical research.

(4) As set forth in 3(5) and 4(3), on receiving an application to continue or make minor changes, as described in the details below, to human stem cell clinical research (hereunder, "continuation"), the institute director must, after seeking opinions from the ethics committee, and subsequently the Minister of Health, Labor and Welfare, and render a decision whether or not to approve said continuation. and at the same time indicate any items necessary to said clinical research.

For research plans in which the ethics committee or Minister of Health, Labor and

Welfare has indicated points of concern or in need of amendment, in the event that the institute director receives an amended or amended version of the research plan from the principal investigator, he/she must inform and the seek the opinion of the ethics committee or Minister of Health, Labor and Welfare regarding the changes, and render a decision whether or not to approve said continuation.

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- 1 Significant changes as set forth in (4) may include any changes to the research plan other than changes to the target medical condition, the type of cell or collection method to be used, or the processing or method of transplantation or administration in the human stem cell clinical research.
 - 2 For human stem cell clinical research conducted in collaboration with other institutions, the decision whether or not to approve by the institute director must be made after seeking the opinion of the ethics committees at each institution involved.
 - 3 For human stem cell clinical research conducted in collaboration with other institutions, when seeking the opinion of the ethics committees at each institution, the institute director must also receive such information as the state of the review, and the informed consent process, etc.
- (5) Measures for serious situations
- 1) When notified of the development of a serious situation relating to human stem cell clinical research by the principal investigator, as set forth in 3(12), the institute director must give instructions regarding taking measures such as analysis of the cause, and rapidly, after seeking the opinion of the ethics committee chair, indicate to the principal investigator whether to stop said clinical research or take other contingency actions.
 - 2) For human stem cell clinical research involving collaboration between multiple institutions for the collection, processing, and transplantation or administration, in the event of a serious situation as set forth in 3(12) and 4(5), the institute director who received the report of the serious situation must instruct the principal investigator to take any necessary actions as described in 1) above, and inform all of the institute directors at the other institutions involved in said clinical research of the serious situation and any actions being taken.
Furthermore, all institute directors must work together to perform the duties set forth in (6) through (12).
- (6) Reports from principal investigators
- In the event of a serious situation, the institute director, in addition to receiving a report from the principal investigator, may, as needed, request a hearing.
- (7) Reporting to the ethics committee

The institute director shall do the following.

- 1) When the institute director has received a report on the state of progress in the human stem cell clinical research from the principal investigator, he or she shall report such information to the ethics committee.
- 2) In cases in which the ethics committee has indicated areas for further consideration or amendment, as set forth in 8 (2) 2), the institute director shall report to the ethics committee any actions taken by the principal investigator in response.
- 3) On receiving a comprehensive report from the principal investigator, the institute director shall rapidly submit a copy of said report to the ethics committee.
- (8) Reporting to the Minister of Health, Labor and Welfare
 - 1) On receiving a report of a serious situation from the principal investigator, as set forth in 3(12), the institute director shall rapidly take the following actions.
 - 1 Inform the Minister of Health, Labor and Welfare of the development of a serious situation, and the nature of the situation
 - 2 Obtain the opinion of the ethics committee regarding the serious situation and after giving instructions regarding stoppage of the clinical research or taking other necessary measures such as analysis of the cause, inform the Minister of Health, Labor and Welfare of the ethics committee opinion and any instructions that have been given to the principal investigator regarding taking measures such as analysis of the cause.
 - 3 After stopping the clinical research or taking other necessary measures, inform the Minister of Health, Labor and Welfare of the results of the actions taken.
 - 2) On receiving a comprehensive report from the principal investigator, the institute director shall rapidly submit a copy of said report to the Minister of Health, Labor and Welfare.
- (9) Instructions to principal investigators

On receiving opinions from the ethics committee or Minister of Health, Labor and Welfare, the institute director shall, as necessary, instruct the principal investigator regarding the taking of measures such as amendment, stoppage, survey, or other necessary actions.

In the event that the ethics committee recommends that human stem cell clinical research be stopped, the institute director must issue instructions to stop said research.
- (10) Record-keeping systems

The institute director must ensure that systems are in place to enable the principal investigator to keep records relating to the human stem cell clinical research in good condition.
- (11) Publication of the research plan

The institute director shall make efforts to publish the research plan and results of the human stem cell clinical research.

(12) Research systems

The institute director must implement research systems appropriate to the conduct of the human stem cell clinical research.

(13) Assignment of hearing Minister of Health, Labor and Welfare opinion

For human stem cell clinical research in which collection, processing, and transplantation or administration take place at multiple institutions, when an application as set forth in (3) or a comprehensive report as set forth in (8) 2) is received from the study leader, an institute director can be assigned by the directors of the other institutes to act as their representative at a hearing of the opinions of the Minister of Health, Labor and Welfare as set forth in (3), or to submit a copy of the comprehensive report, as set forth in (8) 2).

6 Duties as organizational representative

(1) Duties with respect to the protection of personal information

- 1) Representatives of institutions engaged in human stem cell research, or directors of public institutions (hereunder, “organizational representatives”), shall take measures for the protection of personal information when said organization engages in human stem cell clinical research.
- 2) The organizational representative, on recognizing that measures are required to ensure the protection of personal information may inform the institute director of the fact and takes measures as necessary for supervision.

(2) Safety measures for personal information

The organizational representative must take such organizational, personnel, physical and technological measures as necessary and appropriate to ensure the safe management of personal information.

Moreover, out of consideration for the dignity of the deceased and the feelings of their survivors, the organizational representative must put similar organizational, personnel, physical and technological measures as necessary and appropriate to ensure the safe management of information relating to deceased persons to those for other personal information.

(3) Handling complaints and inquiries

In order to ensure the rapid and appropriate handling of complaints and inquiries, the organizational representative must establish a point of contact for complaints and

inquiries, and make efforts to establish procedures and systems for handling complaints and inquiries.

(4) Collection of handling fees

The organizational representative may assess a handling fee for requests for the issue of notifications of the usage objectives of personal information, or the disclosure of held personal information. The amount of such handling fees must be within a reasonable range reflecting the actual costs involved.

(5) Assignment of rights

The organizational representative may assign the rights and duties set forth in (2) through (4) to the institute director or other appropriate person at the institution.

7 Research institution standards

At the following research stages, the research institution must have systems in place to enable it to meet the basic principles set forth in Chapter 1 Paragraph 6.

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For human stem cell clinical research involving collaboration between multiple institutions for the collection, processing, and transplantation or administration, the research must be carried out in strict compliance with the Pharmaceutical Affairs Law (Law 145, 1960), Implementation of autologous tissue for regenerative cell therapy in health care (Health directive 0330, No. 2, 2010) and other relevant regulations.

(1) Institution collecting human stem cells or differentiated cells

The institution at which the collection of human stem cells or differentiated cells takes place must satisfy the following.

- 1) The institution must be managed in a manner sufficiently hygienic for the collection and storage of human stem cells or differentiated cells, and have sufficient knowledge and technology for such work.
- 2) The institution must take measures to ensure the protection of donors' rights.
- 3) For collection involving invasive procedures, the institution must be a medical institution.
- 4) The institution must have an ethics committee in place.

(2) Processing institution

The institution at which processing takes place must satisfy the following.

- 1) The institution must have the facilities and equipment necessary to maintain sterile conditions to ensure survival of human stem cells as suited to the biological properties of such cells.

- 2) The institution must maintain the sterile conditions necessary for the processing and storage of human stem cells, and have the knowledge and technology required for such work.
 - 3) The institution must show consideration in its equipment and procedures to prevent mistakes in the handling of cells.
 - 4) The institution must have an ethics committee in place.
 - 5) The institution must implement education and training of researchers to prevent inappropriate processing of cells.
- (3) Transplanting or administering institution
- The institution at which transplantation or administration takes place must satisfy the following.
- 1) The institution must be a medical institution
 - 2) The institution must have researchers with the ability to perform sufficient clinical observation and testing and analysis and evaluation of the results of transplantation or administration of human stem cells, as well as the facilities and equipment necessary for such purposes.
 - 3) The institution must have researchers with the ability to take measures as necessary for the management of patient symptoms, as well as the facilities and equipment necessary for such purposes.
 - 4) The institution must have an ethics committee in place.

8 Ethics committee

- (1) The ethics committee must satisfy the following.
 - 1) In order to be able to review the human stem cell clinical research from ethical and scientific perspectives, the ethics committee must include the following among its members. It may not however include researchers.
 - 1 Expert(s) in molecular biology, cell biology, genetics, clinical pharmacology or pathology.
 - 2 Clinician(s) expert in the medical condition that is the subject of said research
 - 3 Expert(s) in law
 - 4 Person(s) with insight in bioethics
 - 2) The ethics committee must include both male and female members. It must include multiple members from outside the institution.
 - 3) To ensure fair and proper review, its independence and freedom must be guaranteed.
 - 4) Regulations on the composition, organization, administration and review of the human stem cell clinical research must be established and made public.

- (2) Members of the ethics committee shall perform the following duties
 - 1) In response to a request for opinions from the institute director, the ethics committee shall review the appropriateness of the research plan, and issue its opinions to the institute director as to whether or not its implementation or continuation is appropriate, or raises any points for consideration or amendment.
 - 2) Receive reports from the institute director regarding the progress of the human stem cell clinical research, and issue its opinions to the institute director regarding points for consideration or amendment, stoppage of the research, etc.
 - 3) In cases in which the ethics committee receives a report on measures or amendments taken in response to points for consideration or amendment as described in 1) and 2), the committee shall rapidly review the report and issue its opinions to the institute director as to whether or not its implementation or continuation is appropriate, or raises any points for consideration or amendment.
 - 4) In cases in which the ethics committee receives a report of a serious situation from the institute director, as set forth in 5(5), the committee shall rapidly issue its opinions to the director regarding the measures taken in response, such as analysis of causes.
 - 5) As deemed necessary, the ethics committee may request that the institute director conduct a review of the human stem cell clinical research during its implementation or following its conclusion to ensure its appropriateness and credibility.
 - 6) A record must be kept of the ethics committee review process for at least 10 years from the submission of a copy of the comprehensive report. This shall be made public, in principle, with the exception of those items which represent a risk of interfering with protection of personal information, research originality or intellectual property.

Paragraph 2 Opinions from Minister of Health, Labor and Welfare, etc.

1 Opinions from Minister of Health, Labor and Welfare

- (1) As set forth in 1, 5(3) and 1, 5(13), in response to a request for opinions from the institute director, the Minister of Health, Labor and Welfare shall review the appropriateness of the research plan, and issue its opinions to the institute director as to whether or not its implementation or continuation is appropriate, or raises any points for consideration or amendment.
- (2) When requesting an opinion from the Minister of Health, Labor and Welfare, the institute director must submit the following documents:
 - 1) Research plan and attachments
 - 2) Documents showing the process of review by the ethics committee
 - 3) Regulations set forth in Paragraph 1, 8 (1).4)

- (3) As set forth in 1, 5(3) and 1, 5(13), in response to a request for opinions from the institute director, when reviewing new items relating to the human stem cell clinical research the Minister of Health, Labor and Welfare shall seek the opinion of the Health Science Council.

2 Opinions from the Minister of Health, Labor and Welfare on serious situations

In cases in which the Minister of Health, Labor and Welfare receives a report of a serious situation from the institute director, as set forth in 1, 5(8)1), the committee shall rapidly issue its opinions to the director regarding the measures taken in response, such as analysis of causes.

3 Review by the Minister of Health, Labor and Welfare

When issuing opinions as set forth in 1(1) and 2, the Minister of Health, Labor and Welfare may, as deemed necessary, request documents other than those set forth in 1(2), and, with the acknowledgment of the institute director, conduct a review of the research institution, or other such reviews as necessary.

Chapter 3 Collection of human stem cells and differentiated cells

Paragraph 1 Protection of donor rights

1 Donor selection

Selection of donors shall be done in a manner exercising careful consideration for such factors as symptoms, age, competency for giving consent from the perspective of protecting such persons' human rights.

2 Informed consent

Persons providing explanation shall give sufficient explanation of the items listed in 3, below, using written documents to prospective donors (including proxies; also in 3, below) of human stem cells or differentiated cells, and after confirming their understanding, obtain informed consent. The person providing the explanation should in principle be a physician, familiar with medical procedures involved in the collection, but may be a person other than a physician if the principal investigator determines that such person is appropriate to provide such explanations.

3 Items to be explained to prospective donors or proxies

The person providing explanation shall, as part of the process described in 2, above, give sufficient explanation of the following items to prospective donors or their proxies using plain and easily understandable language.

- 1) The objective and significance of the human stem cell clinical research
- 2) The name of the institution conducting the human stem cell clinical research
- 3) The predicted risks and effects of the human stem cell clinical research (including results of previous research)
- 4) The freedom to decline participation as a donor, and assurance that refusal to participate in such will carry no negative consequences
- 5) The freedom of prospective donors to withdraw consent at any time, even after consenting to serve as a donor
- 6) That the donation is made gratis, without financial compensation. This does not limit, however, reimbursement of costs associated with the donation.

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Expenses that may be reimbursed, as set forth in 6), above, after receiving ethics committee approval, include transportation costs relating to the donation.

- 7) Measures in place to compensate for any damage to health (when compensation is made in conjunction with human stem cell clinical research, that shall be included as such compensation)
- 8) Other necessary items relating to the protection of research subjects' personal information, etc.

4 Informed consent from proxies

Proxies may provide informed consent for collection of human stem cells or differentiated cells only in those cases in which the following conditions are met.

- 1) It would be difficult within the conduct of human stem cell clinical research to obtain informed consent directly from the individual, and the rationale for collection of human stem cells or differentiated cells is deemed reasonable, and has been reviewed from an ethical perspective by the ethics committee and approved by the institute director.
- 2) The proxy is a person judged capable of representing the intents and best interests of the research subject, and for whom a record of the relationship with the prospective research subject is made at the time of obtaining the informed consent, to be kept along with the consent form.
- 3) In cases in which the prospective donor is a minor 16 years of age or older and capable of understanding explanations relating to the participation in the human stem cell

clinical research, consent shall be obtained from the minor as well. In cases in which the minor is younger than 16 years of age, the minor's understanding shall be obtained.

5 Use of human stem cells or differentiated cells extracted in surgical procedures, etc.

Human stem cells or differentiated cells extracted in surgical procedures, etc. can only be used with the informed consent of the donor, as outlined in 1 to 4, above. Moreover, surgical procedures and other aspects of medical care may not be altered to give priority to the collection of human stem cells or differentiated cells.

6 Cadaveric donations

When human stem cells or differentiated cells are collected from a cadaveric donor, informed consent as described in 2, above, must first be obtained from a member of the deceased person's surviving family. Such collections can only be made providing the deceased person did not object to the donation of human stem cells or differentiated cells when alive.

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Surviving family members as described in 6 may include spouses, adult children, parents, adult siblings or cousins, aunts, uncles, cohabitating relatives or others deemed equivalently close relations.

7 When donors are also transplantation or administration recipients

When a donor is to receive transplantation or administration, surgery may be performed to collect human stem cells or differentiated cells.

Paragraph 2 Safety measures in processing stages

1 Donor selection criteria and eligibility

- (1) In order to determine prospective donor eligibility for the collection of human stem cells or differentiated cells, researchers, etc. should confirm their previous history in light of the usage objective, and perform diagnostic tests and examinations. In particular, interviews and tests (serum, nucleic acid amplification, etc.) must be conducted to determine whether or not the prospective donor carries hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), adult T cell leukemia, or parvovirus B19. In addition, tests for infection by cytomegalovirus and EB virus should be performed as necessary.

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Donor screening is not required for autologous stem cells, but consideration should be given to testing for HBV, HCV, and HIV to mitigate risks of cross-contamination during processing and for the safety of processing staff.

- (2) Researchers shall test for the following by confirmation of medical history, examination and testing, and determine donor eligibility giving consideration to factors such as whether or not they have received blood transfusions or transplantations.
 - 1) Infection by syphilitic treponema, chlamydia, gonorrhea, tuberculosis or other bacterial infections
 - 2) Sepsis, or potential sepsis
 - 3) Malignant tumors
 - 4) Severe endocrine metabolic disease
 - 5) Collagen or blood disease
 - 6) Liver disease
 - 7) Suspected transmissible spongiform encephalitis or dementia
- (3) Selection of diagnostic tests and testing should be done using the most appropriate methods available. Testing methods should be continuously reviewed and updated to reflect the latest scientific findings and technology.
- (4) When screening donors, researchers, etc. should allow for a window period as appropriate to the test items and methods, and re-test at appropriate time points to the extent possible.

2 Ensuring proper collection procedures

- (1) When collecting human stem or differentiated cells, researchers must take measures necessary to prevent against contamination by microbiological or other agents during the collection process. Collected human stem or differentiated cells should also be tested as appropriate for the presence of microbiological agents or other contaminants. Testing methods should be constantly reviewed and revised with respect to the latest scientific findings and technologies.
- (2) When collecting human stem cells or differentiated from a cadaveric donor, researchers should take special care to act with respect for the donor.

3 Record-keeping

- (1) Researchers, etc. shall keep records of such items as the results of tests and inspections made for donor screening, the details of the collection procedure, and tests performed on collected human stem cells and differentiated cells.

Moreover, such records should be marked so as to make it possible to determine the institute and date at which the collection was made.

- (2) Any relevant ethics committee meeting minutes and the items explained and consent forms must be attached to said records.
- (3) The records described in (1) and attachments described in (2) shall be kept for at least 10 years following the submission of the comprehensive report.
- (4) The principal investigator must establish systems as necessary for obtaining information such as whether the donor develops a late-onset infection even after the time of the donation of human stem cells or differentiated cells.

Moreover, samples such as fractions of human stem cells or differentiated cells collected must be kept for an appropriate period so as to enable the determination of the success or failure of stem cell processing, or the cause if a research subject who has received a transplantation or administration develops an infection.

Chapter 4 Safety measures for human stem cells at the processing stage

Paragraph 1 Safety measures at the processing stage

1. Quality control

- (1) The processing institution that handles human stem cells and the final preparation must establish a quality control system adapted to the properties of human stem cells and the final preparation.
- (2) The processing of stem cells must take place using facilities and equipment needed for work such as the taking delivery of primary materials, preparation processes, intermediate preparations, and the storage of final preparations, and the work areas for such activities must be separate from those used for other work activities. However, dedicated facilities may not be necessary for certain procedures, such as for example the processing of harvested human stem cells by minimal manipulation under sterile conditions for immediate transplantation or administration to a donor in areas of research-grade sterility, such as surgical theatres.
- (3) The processing institution must maintain facilities and equipment used in the processing of human stem cells in sterile conditions, and keep a record of its efforts to maintain such conditions, such as through maintenance and inspections.
- (4) The processing institution must not culture human stem cells from multiple donors together in the same culture equipment, and must avoid mistakes in handling and the

transmission of infection through measures such as not storing cells under conditions permitting of cross-contamination.

2. Standard operating procedures

Researchers, etc. shall create a set of written standard operating procedures to be followed for each processing work activity. To create the standard operating procedures preliminary operations for evaluation and inspection for processes such as sterilization shall be implemented. Procedures shall also be established for the handling of emergencies, such as accidents.

3. Taking delivery of primary materials, such as human stem cells or differentiated cells

At the time of taking delivery of primary materials, such as human stem cells or differentiated cells, researchers must confirm that the materials meet necessary standards as recorded in Chapter 3.2.3(1).

4. Testing and inspection when taking delivery of reagents

Researchers must establish quality standards suited to usage objectives for reagents used in processing, and test and inspect all reagents at the time of delivery.

5. Testing and inspection of final preparations

- (1) Researchers, etc. shall conduct tests to confirm the properties of human stem cells to be used in human stem cell clinical research in the final preparation. Quality standards for cells to be used in such research should be developed from the results of such tests, and used in testing and inspection. Moreover, quality standards should be established, as necessary, for human stem cells during processing, and testing and inspections implemented.
- (2) Quality control of final preparation shall include, for example, the following. Note that these are only examples for the purposes of illustration, not an exhaustive list of all required tests; the final set of items necessary for test and inspection must be determined in accordance with such aspects as the properties of the human stem cells, the research objective, and scientific knowledge. Specifications (standard criteria) can be set provisionally at the start of the research, and should be reviewed as said research progresses to bring them into line with quality characteristics relevant to clinical safety and efficacy.

- 1) Rates of cell recovery and survival
- 2) Validation
- 3) Cellular purity
- 4) Cell-derived bioactive compounds other than those that are the subject of the research
- 5) Impurities arising from processing
- 6) Sterility and mycoplasma testing

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Considering the possibility of cases in which the tests described in 6) are founded to be positive after administration to research subjects, clear contingency measures should be in place in advance.

- 7) Endotoxin testing

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Criteria developed with reference to Japanese Pharmacopeia must be determined for the tests described in 7).

- 8) Testing for viruses, etc.
 - 9) Efficacy testing
 - 10) Titer testing
 - 11) Tests for mechanical compatibility
- (3) In cases in which the final preparation includes components other than human stem cells (such as extracellular matrix, medical material, scaffolding, basement membrane, fiber or microbeads), findings regarding the quality and safety of such components shall be made clear.

6 Exclusion of risks of microbiological contamination

Researchers shall exclude risks of contamination, such as by microbiological agents, by a combination of measures appropriate to the human stem cells' derivatives, properties and processing methods.

- (1) Confirmation of donor screening records at the time of taking delivery
- (2) Prevention of contamination during processes such as cell culture for processing purposes and administration of reagents
- (3) Testing and inspection as necessary at each stage of processing
- (4) Introduction of methods for inactivation and elimination

7 Quarantine, shipment and delivery

Research shall take quality control measures, such as temperature control, at the time of shipment.

8 Record-keeping during processing

- (1) Researchers, etc. shall keep records of all manipulations, tests and inspections as well as information relating to shipment.
- (2) Researchers, etc. shall keep records as set forth in Chapter 3 Paragraph 2.3(1), so as to make it possible to confirm processing, testing, inspection and shipment records for each lot.
- (3) Researchers shall keep all records as described in (2) for at least 10 years from the date of submission of the comprehensive report.

9 Latest technology

Researchers, etc. should review and update processing, testing and inspection methods as necessary to reflect the latest scientific findings and technology.

Paragraph 2 Management systems in processing stages

- 1 The principal investigator shall familiarize the researchers with these guidelines at the start of processing, and periodic conduct the following types of training.
 - (1) Knowledge of stem cells
 - (2) Knowledge and techniques for the safe handling of stem cells during processing
 - (3) Knowledge and techniques relating to facilities and equipment
 - (4) Knowledge and techniques relating to safety during processing operations
 - (5) Knowledge and techniques for use in emergencies
- 2 The principal investigator overseeing the processing shall implement periodic health checks for researchers, and persons not appropriate for the handling of human stem cells shall not be allowed to perform processing procedures.
- 3 Immediately prior to the collection of human stem cells or differentiated cells, or the processing of human stem cells, persons engaged in the handling of agents such as microbiological organisms that pose a risk of infection or contamination or those that pose a potential risk of undesired effects on human stem cell purity or safety shall be prohibited from entering the work area.
- 4 The principal investigator in charge of processing shall give consideration in advance procedures for the prevention and treatment of infection within the work area.
- 5 In cases when infection is suspected within the work area, the principal investigator in charge of processing shall immediately implement health checks for researchers and other appropriate measures.

- 6 During implementation of researcher health checks and taking of serum samples, care shall be exercised to protect researchers' personal information and consideration shown for their human rights.

Chapter 5 Transplantation or administration of human stem cells

Paragraph 1 Human rights of research subjects

1 Selection of research subjects

Selection of research subjects shall be done in a manner exercising careful consideration for such factors as symptoms, age, competency for giving consent from the perspective of protecting such persons' human rights.

2 Informed consent

Persons providing explanation shall give sufficient explanation of the items listed in 3, below, using written documents to prospective research subjects (including proxies, also in 3, below) in human stem cell clinical research involving transplantation or administration, and after confirming their understanding, obtain informed consent.

3 Items to be explained to prospective research subjects

The person providing explanation shall, as part of the process described in 2, above, give sufficient explanation of the following items to prospective research subjects using plain and easily understandable language.

- 1) The objective and significance of the human stem cell clinical research
- 2) The name of the institution conducting the human stem cell clinical research
- 3) The predicted risks and effects of the human stem cell clinical research (including results of previous research)
- 4) Comparison of the predicted risks and effects of the human stem cell clinical research with other treatment options, including the absence or presence of treatment and the nature of such treatments
- 5) The freedom to decline participation as a research subject in human stem cell clinical research, and that refusal to participate in such will have no negative effect on the person, and that he/she will be able to continue to receive treatment
- 6) The freedom of prospective research subjects to withdraw consent at any time, even after consenting to transplantation or administration
- 7) Measures in place to compensate for any damage to health resulting from said research

- 8) Other necessary items relating to the protection of research subjects' personal information, etc.

<Details>

Information on other necessary items relating to the protection of research subjects' personal information, etc., as set forth in 8), includes information on any financial burdens imposed on the research subjects.

4 Informed consent from proxies

Proxies may provide informed consent for transplantation or administration within the course of human stem cell clinical research only in those cases in which the following conditions are met.

- 1) It would be difficult to obtain informed consent directly from the individual and the rationale for performing transplantation or administration during the course of human stem cell clinical research is deemed reasonable, and has been reviewed from an ethical perspective by the ethics committee and approved by the institute director.
- 2) The proxy is a person judged capable of representing the intents and best interests of the research subject, and for whom a record of the relationship with the prospective research subject is made at the time of obtaining the informed consent, to be kept along with the consent form.
- 3) In cases in which the prospective research subject is a minor 16 years of age or older and capable of understanding explanations relating to the participation in the human stem cell clinical research, consent shall be obtained from the minor as well. In cases in which the minor is younger than 16 years of age, the minor's understanding shall be obtained.

Paragraph 2 Safety measures for transplantation and administration

1 Information management relating to human stem cells

The principal investigator shall manage information relating to the human stem cells, such as donor screening, results of tests and inspections of the final preparation, processing number, and lot number.

<Details>

For uses of non-autologous homologous cells or cells co-cultured with non-human-derived materials, the principal investigator assess the attendant risks, and shall conduct tests for contamination by viruses and infectious agents.

2 Keeping of research subject test records, etc.

The principal investigator shall maintain the final preparation for an appropriate period to allow for determinations to be made as to whether or not any future infections in research subjects are attributable to the human stem cell clinical research, and further to maintain results of serum tests from human stem cell clinical research subjects prior to transplantation or administration, as well as records pre- and post-transplantation or administration of human stem cells for at least 10 years following the submission of the comprehensive report.

<Details>

In cases in which the final preparation as set forth in 2 is a hybrid that includes non-human materials, the final stage human stem cells shall be maintained for an appropriate period.

3 Assessment of research subject information

- (1) In the event of adverse events such as pathogenic infection of a research subject, the principal investigator shall take appropriate measures as needed to assess the relevant information, or, in cases in which the problem is attributable to the final preparation, to assess the research subject's health status.

<Details>

The principal investigator may list the nature, identifying code, processing number and other information relating to transplanted or administered human stem cells on a research subjects medical chart in order to fulfill the objectives described in (1), above.

- (2) In order to take the measures described in (1), above, the principal investigator should seek the cooperation of research subjects in providing and maintaining the necessary information, and should give instructions as needed to researchers, etc., in advance.

Chapter 6 Miscellaneous

Paragraph 1 Review

To account for scientific advances, and changes in social conditions regarding the handling of human stem cells, these guidelines may be reviewed as necessary, or every five years. At such times, the Ministry of Health, Labor, and Welfare (MHLW) will convene a committee of experts in medicine and bioethics to review amendments in an objective and comprehensive manner, and obtain approval.

Paragraph 2 Effective date

These guidelines go into effect as of November 1, 2010.

Paragraph 3 Transitional measures

Human stem cell clinical research begun prior to the enactment of these guidelines may be conducted in compliance with the previous guidelines.