

GUIDELINE ON ETHICAL ISSUES IN APPLICATION OF HUMAN TISSUE TO MEDICAL PRACTICE

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I. INTRODUCTION

The mission of transplantation medicine is to serve for protecting lives and improving the quality of life. Transplantation medicine has long pervaded Japan as it has internationally. Such transplantation includes kidney, heart, lung, pancreas, cornea, skin, bone, bone marrow, cardiac valve, etc.

Along with common ethical issues shared with regular medical practice, transplantation has a specific aspect in that it always requires donors of organs and tissues. Thus, the ethical consideration for both donors and recipients are absolutely vital in transplantation. Regarding organs, the *Organ Transplant Act* raises the legal considerations for a range of ethical issues relating to brain-death organ transplantation. On the other hand, there is no authoritative document concerning the ethical issues in tissue transplantation, therefore preparation of a guideline has been urgently required. Starting from these perspectives, JSTT has drafted the ethical guidelines for transplantation of human tissue retrieved from a deceased donor. Fortunately, there is a transcript of a tentative draft drawn up by the Special Committee (tissue transplantation section) of the Public Health Council of the former Ministry of Health and Welfare (MHW) (Chairman: Prof. Kikuo Nomoto, Dept. of Immunology, Kyushu University), held in fiscal 1999, in which the ethical policy for tissue transplantation has been described. In developing our guidelines, JSTT has taken the former MHW's policy draft as our basis and reflected changes of social conditions made since then.

Hereinafter, the presented contents are guidelines composed by the ethical committee of JSTT. Yet JSTT expects an extended application of this guideline for research at universities and laboratories, and for distribution to commercial organizations, with due consideration to Circular No. 1314 of "Guidelines for safety and quality in medical products manufactured from human/animal derived materials" issued by the Pharmaceutical and Medical Safety Bureau of the former MHW

At present, human tissues like skin, bone, ligament, cardiac valve, blood vessel, and pancreatic islet cell are procured and stored for medical application in Japan. Some of these tissues have organized banking systems managing storage and distribution. On the other hand, there is no law regulating tissues retrieved from a deceased donor, (article 5 of the Organ Transplant Act and article 1 of its Enforcement Regulation only deal with organs for transplantation). However, in article 11.6 of the basic guidelines which were promulgated by the MHW is described as "transplantation of human tissues is to be conducted as medical practice with consent of the donor, who did not object during his/her life to donating organs after death, and that of his/her next-of-kin, with due consideration over the social and medical standards."

This guideline provides the conditions to be met in application of human tissues for research and other purposes, as well as presenting the ethical and safety requirements for using tissues for transplantation. A tissue bank, where human tissues are utilized for transplant or research, is also required to pay sufficient attention to retain social responsibilities and transparency in its management, and must maintain ethical adequacy and safety. (Reference: JSTT Guideline on safety, storage, and application of human tissues in medical practice)

JSTT expects that our guideline would promote sensible management of tissue banks, and also promote social understanding and trust toward the use of human tissues. Please note

that there is a section for the definition of terms at the end of this document.

II. BASIC POLICY

This guideline presents ethical measures in transplantation and research, conducted by medical institutions, research laboratories, or other organizations using human tissue retrieved principally from deceased donors. In conducting such practice, human rights and dignity must be always respected; activities of a tissue bank must maintain the social responsibility and transparency, and the safety of those who are engaged in the practice.

III. TISSUES SUBJECT TO THIS GUIDELINE

Human tissues subject to this guideline are skin, cardiac valves, great vessel, peripheral vessel, bone, ligament, eardrum membrane, auditory ossicles, islets of Langerhans, trachea, bronchi, and retina, which are retrieved from deceased donors after the cardiac arrest. Any tissue retrieved from a living donor is not included here.

IV. COMPLIANCE WITH THE BASIC PRINCIPLES IN APPLICATION OF HUMAN TISSUE

On utilizing human tissue, one must comply with following 7 fundamental principles to secure ethical adequacy and safety.

- A. All donation must be done under freewill of the donor and his/her next-of-kin. All human tissues must be donated under the complete freewill of the donor, or by that of his/her next-of-kin if donated after death. In the process of determination, undue pressure of any kind should not influence the decision of the next-of-kin.
- B. Informed consent of the donor/recipient
The donor party must receive sufficient information of the process of donation, procedures of tissue retrieval and how the tissue would be used, before making the decision to donate. The recipient party must be given sufficient information of the efficacy and potential risks of human tissue transplantation, on deciding to undergo the transplantation.
- C. Retaining social/public responsibilities, and the dignity of the donor
Donation of human tissue is a sublime act done for the society with good will. A tissue bank and transplant institution must treat donated tissue with secured respect for the dignity, will and good faith of the donor and keep public responsibility. The donor cannot assert any right on the donated tissue after the donation.
- D. Donation should be done on a non-profit basis
Donation of human tissues is to be carried out on a non-profit basis. Financial reward must not be offered on donation of tissues. Operating as a non-profit organization, a tissue bank cannot claim or receive financial gain over human tissue distribution.
- E. Maintaining the safety and efficacy of donated human tissue
Those who engaged in banking and transplantation of human tissue must be

fully aware of the purpose of human tissue donation, which is for the treatment of a recipient. The safety and efficacy in retrieval, processing, storage and transplantation of human tissue must be maintained. The interested parties should also be vigilant to the potential risks of transmittable infection through transplantation, and must endeavor to collect information of such risks.

- F. Protection of personal data
All personal data must be protected for donor and recipient confidentiality. Personal data of the donor and recipient party must be protected.
- G. Disclosure of the information
As a social and public organization, a tissue bank is obliged to make its activities public, while adequately protecting personal data.

V. THE BASIC PRINCIPLES IN RETRIEVAL OF HUMAN TISSUE

The retrieval of human tissue must comply with the following fundamental principles to promote the safety and ethical adequacy.

- A. Informed Consent Required at the Retrieval of Human Tissue
 - 1. On retrieval of human tissue for transplant and other purposes, information must be given with sufficient consideration for the donor. Prior to the retrieval, a written consent of donation issued voluntarily by the donor must be obtained. More specifically, the donor's next-of-kin must receive sufficient explanation over the 4 points with a written form and the document must be given to the donor party.
 - a) The process of donation, procedures for tissue retrieval, and the state of donor after the donation.
 - b) The purpose of donation. The primary purpose of tissue donation is for clinical application. In case it is not to be used for transplantation, the destination of the tissue must be clarified. (i.e. used for research, education, training purposes at a university, research laboratory, or use for other purposes.)
 - c) Disclosure of donor screening tests results: The result of donor screening tests is to be disclosed to the donor's next-of-kin on request.
 - d) Treatment of human tissue after its retrieval. Recovered tissue shall not be returned to the donor's next-of-kin, except in the case duly approved by the ethical committee, etc.
 - 2. On providing explanation about tissue donation to the donor's next-of-kin the will and intentions of the donor's next-of-kin must be always respected. When met by a rejection, even in the middle of an explanation, the donor party are able to abandon the explanation. It should be also made clear that the donor's next-of-kin holds the right to refuse and that no disadvantage should occur to the donor's next-of-kin.
 - 3. In order to avoid the undue influence of the clinical relationship, the explanation shall be given to the donor's next-of-kin by neutral personnel,

such as a coordinator, who works for a tissue bank. If such arrangement is unavailable, it is desirable that a person, who has (or ever had) no involvement in the donor's medical attendance, provides the explanation.

B. Procedures in the Retrieval of Human Tissue

1. Retrieval of human tissue for transplant is allowed to be performed only after the donor party has been fully informed of the retrieval process, and the following requirements have been met.
 - a) The deceased donor has consented during his/her life, or the close relatives have consented.
 - b) It must be a socially admissible procedure: for instance, the sense of respect toward the dead is maintained throughout the process.
2. When a donor expressed objection during his/her life, retrieval of any tissue is not allowed even though the next-of-kin grant consent.
3. A physician must procure human tissue. Maintaining respect for the dead throughout the process is especially important.
4. The retrieval of human tissue should be performed under aseptic conditions and contamination by any micro-organism during the retrieval process must be minimized.
5. Those who are engaged in human tissue banking must not provide, offer, request or promise any financial consideration to the donor party for receiving or having received a human tissue donation.
6. Those who engaged in human tissue banking must strictly protect and keep confidentiality of all personal data of the donor. Such data or information should not be disclosed to anyone but those who are involved in the tissue banking operation.

C. Requirements in Donor Screening Tests

The retrieved tissue should not be used if the donor fails the donor suitability review. It is necessary to conduct a detailed interview, inspection and palpation of the donor. Interviewing the donor's next-of-kin to obtain the medical/social history of the donor is also required. Review of the medical record, and the pathological findings, if an autopsy is performed, is required. Current serology tests must be performed on a blood sample to evaluate the serology panel. Criteria and serology tests must be always kept current, in accordance with technical and academic advancement, and new findings about infectious diseases. It may be desirable to involve a group of experts, such as related academic societies, in the process of evaluating the information on infectious diseases, etc.

VI. HUMAN TISSUE DISTRIBUTION TO/APPLICATION AT A FACILITY FOR TRANSPLANTATION

- A. When a tissue bank distributes human tissues to a transplant facility, the distribution must be conducted in accordance with a written standard. Selection of a recipient must be done carefully.
- B. A tissue bank must provide information to a transplant facility about the criteria, procedures, and results of donor screening tests.
- C. All data must maintain confidentiality while permitting traceability. All data must be kept at the tissue bank for at least 10 years, and as long as possible thereafter.
- D. A transplant facility must obtain consent from the recipient party prior to the transplantation. To obtain consent, physicians of the transplant facility should give sufficient information to the recipient on the safety, efficacy and potential risks in human tissue transplantation.
- E. Upon performing transplantation, the transplant facility must keep the record of the source bank name, identification number of transplanted human tissue, etc., in order to track the tissue, if necessary.
- F. Those who are engaged in human tissue banking and transplantation must strictly keep confidentiality of all data of the recipient and any other information, which the recipient wishes to withhold. Data or information should not be disclosed to any third party, except to regulatory agency(ies), if required. All personnel are responsible for controlling and managing such confidential data.
- G. As a non-profit and public organization, a tissue bank must not receive, seek, or promise any financial consideration from a transplant facility or a patient for human tissue distribution. However, reasonable expenses for travel, communication, coordination, retrieval, storage, and transportation, should be recovered.

VII. APPLICATION OF HUMAN TISSUE FOR RESEARCH/EDUCATION/TRAINING AND/OR OTHER PURPOSES AT A LABORATORY OR A COMMERCIAL COMPANY, ETC.

- A. Application for transplantation is the primary purpose of receiving donated human tissue at a tissue bank. However, when the donated tissue is not suitable for transplantation, or the donor party wishes it to be used for purposes other than transplantation, it may be used in research/education/training, etc., at a research laboratory or by a researcher (including a commercial company or organization) with the informed consent of the donor party to that effect.
- B. The definition of ‘research’ ‘education’ and ‘training’ mentioned herein are to be defined as follows: ‘Research’ is defined as a medical research activity for clinical advancement led by organizations like JHSF (Japan Human Science Foundation), research laboratories of universities, medical institutions, or scientists and researchers of a commercial company and other organization. ‘Education’ and ‘Training’ indicate a practice or preparation for the technicians of tissue banks for development and learning of tissue processing techniques.
- C. When a tissue bank distributes tissue to a research laboratory or a commercial

company, etc., for research/education/training, it is necessary to have prior confirmation and approval by the ethical committee about the legitimacy of the purpose.

- D. Where a commercial company or organization receives human tissue from a tissue bank for other purposes than research/education/training, such organization must be a manufacturer or developer of biological medical products. When the tissue product is distributed, it must have prior confirmation of the legitimacy of the purpose.
- E. On receiving tissue from a tissue bank, the company or organization must record the date of receipt, the source bank name, and the purpose of use, and archive such records and information.
- F. When a tissue bank distributes tissue for a commercial company or other organization, it is necessary to have prior confirmation of the legitimacy of the purpose. The name of the company or organization and the quantity of tissue to be distributed should also be recorded and archived at the bank.
- G. A tissue bank operates as a non-profit organization, and must not receive any financial consideration for the human tissue distribution, even when the tissue is received by a commercial company or organization. However, reasonable expenses for retrieval, storage, and transplantation, can be claimed.
- H. Requirements for a commercial company or organization
 1. It must fulfill the requirements set in this JSTT guideline for utilization of human tissue, and obtain approval from JSTT to receive human tissue.
 2. It guarantees that its activity and management comply with “*the principles in handling and use of tissue/cell derived medical materials*” (issued by the Pharmaceutical and Medical Safety Bureau of the former MHW/26 December 2000)
 3. It is a member of JSTT.

VIII. MANAGEMENT OF A TISSUE BANK

In the management of a tissue bank, the bank is aware that human tissue donation is an act of goodwill for society, and that the safety of tissue and the distribution for transplantation is stable and efficient.

- A. A tissue bank should be a responsible non-profit-organization with a clear identification of the chief executive. When a number of medical institutes cooperate as a joint tissue bank, the activities and management of such bank must be done under mutual consent and responsibility of every participant.
- B. The framework of a tissue bank and its operating system should be clear and prepared in written form.
- C. The system to guarantee the proper retrieval of human tissue should be developed in an organized manner.

1. The approval of the ethical committee should be obtained prior to the retrieval of human tissue. In case the retrieval of tissue is conducted at a medical institute, which does not have the qualification of a tissue bank, cooperation and understanding of such institute on the above issues is required.
 2. The record, which shows the procedures and processes of tissue retrieval, should be kept and stored at a tissue bank, and should be regularly audited by an internal or outside ethical committee.
- D. A tissue bank should have personnel who manages and controls personal data and confidential information of the donor and the recipient party. A clear structure of control and handling of such data and information must be designed and initiated.
 - E. After distribution of tissue for transplantation, the tissue bank must collect and manage follow-up (prognostic) data and information of the recipient.
 - F. A tissue bank should have personnel in charge of quality control for retrieval, processing, and storage of human tissue. Cooperating with related organizations and institutions should provide regular opportunities of education and training for the technicians who conduct processing and storage of tissue.
 - G. A tissue bank must maintain the transparency in management, prepare a written record, which shows the implementation and performance of the tissue bank (variety, volume, storage status, and application record, etc., of the tissue procured) and make it available to the public on request at any given time.
 - H. A tissue bank must have its own organization or committee for decision making on management, such as institutional ethical committee, etc. For an existing medical institution, the ethical committee of the institution may concurrently work as that of the tissue bank and also may evaluate the process of tissue retrieval. The ethical committee may also give judgement and permission when the tissue is not used for transplantation and is to be applied for other purposes, such as research, education and training, etc.
 - I. The ethical committee, as defined above should set ethical standards to supervise the entire operation of the tissue bank, and make the standards known and understood to every personnel engaged in the operation.
 - J. When a tissue bank claims to cover the costs for distribution (i.e., transport, process, manpower, etc.) to those who received the tissue, the bank must always maintain its non-profit status.

The operation of a human tissue bank naturally requires involvement of members of the public. Thus, a public and social understanding toward its operation is vital to establish a tissue banking system. Every member of tissue banks and all other interested parties must strictly comply with the requirements and standards presented in this guideline, and should always be vigilant in maintaining the ethical adequacy and the safety in one's operation and activities. Offenders against these guidelines will be subject to severe punishment imposed

by JSTT.

IX. CLOSING REMARKS

This guideline has been composed primarily for existing scheme of human tissue application in transplantation. JSTT also expects the guideline to present the ethical principles for those who plan to organize a tissue bank in the future. On composing the guideline, JSTT has taken into account other potential aspects, with advancement of technology in regenerative medicine, the utilization of human tissue may go beyond transplantation and into further range of applications leading to the possibility of commercial or industrial utilization of human tissue, and that there is a prospect of a wide use of new findings provided through studies conducted with human tissue.

X. DEFINITIONS OF TERMS

BANKING

A system consisting of retrieval, storage and distribution of human tissue retrieved from a deceased donor. It is the collective term of such activities.

DONOR

A person (has potential to) donates human tissue for transplantation and other applications.

DONOR PARTY

The donor, member(s) of his/her family and close relatives, and next-of-kin, who can give consent to the donation of tissue, as defined in this guideline.

DONOR SCREENING TEST

A series of tests, examinations, and determination to evaluate if a donor fulfills the donor eligibility for tissue transplantation.

HUMAN TISSUE

Tissue retrieved from a deceased and living donor primarily for transplantation. Among such human tissues to be subjected to this guideline are those that banks are already distributing for transplantation: which are skin, bone, ligament, cardiac valve, vessel, eardrum membrane, and auditory ossicles. The guideline shall also include cells of liver, islets of Langerhans, and cells from other tissues, as they are likely to be distributed through tissue banks in the future. The guideline, however, shall exclude any components otherwise stipulated in laws or other legal acts pertaining to them.

INFORMED CONSENT

A spontaneous agreement to donate or receive human tissue, having been given sufficient information on donation/receiving of human tissue, i.e. purpose, procedures, prospects, and potential risks.

MANAGEMENT of TISSUE BANK

All the operations and activities dealt in a tissue bank: i.e. retrieval, processing, tests, storage, distribution and handling of data and information of human tissue.

MINIMAL MANIPULATION

The process applied to human tissue, of not damaging its original characteristic or function of the tissue. The process includes cutting, cleansing with antibiotic agent, sterilizing with gamma ray or heating, cell separation, and frozen/cryopreservation, etc.

RECIPIENT

A patient, who received treatment with transplanted human tissue, or who has been diagnosed that he/she has a clinical need for human tissue transplantation.

RECIPIENT PARTY

The recipient and his/her next-of-kin

STERILIZATION OF TISSUE(S)

Inactivation of bacteria, fungus, and viruses, etc., by processing with heat, antibiotics, etc.

TISSUE BANK

A non-profit organization founded and operated by a medical institution or a group of medical institutions, which plays the central role of human tissue banking system. In addition, an institute or organization, a hospital or its equivalent where the donor was (is) admitted, is also included as a constitutional member in the tissue banking operations.