H.U. Group Research Ethics Guidelines

(Objectives)

Article 1 These guidelines pertain to the establishment of an ethics review committee and its basic advisory functions for the review of R&D and clinical tests using samples collected from human subjects and information obtained from the samples, including test results, diagnosis, and medical treatment, from the perspectives of ethics and science. These guidelines shall apply to H. U. Group Holdings, Inc., (H.U. Group Holdings), its subsidiaries and affiliates (H. U. Group Holdings, its subsidiaries, and affiliates collectively referred to hereafter as H. U. Group Companies)

(Establishment)

Article 2 The representative director and president of H.U. Group Holdings (Committee Organizer) shall establish the H.U. Group Ethics Review Committee (Committee) as a body to conduct independent, neutral, and fair reviews of R&D and clinical tests conducted within H.U. Group Companies from perspectives of ethics and science.

(Structure)

Article 3

1. The Committee shall consist of at least five men and women, selected by the Committee Organizer from among natural science experts, including experts in medicine and medical care, humanities and sociology experts, including experts in ethics and law, and individuals capable of expressing their opinions from a general stance, including the stance of research subjects.
2. At least three members referenced in the preceding paragraph shall be external members.
3. The three external members referenced in the preceding paragraph may be selected from persons who have been employees at H.U. Group Companies in the past; however, such individuals must have left the employment or retired from H.U. Group Companies at least three years prior to their appointment.

(Committee Member Term of Service)

Article 4

1. The term of service for Committee members is two years. However, this shall not prevent members from being reappointed.
2. Members may retire from the Committee during their term of service in the event of extenuating circumstances.

(Committee Chair)

Article 5

1. The Committee Organizer shall appoint the committee chair.
2. The Committee chair shall represent the Committee and shall serve as chairperson for the Committee. However, the attending members may appoint a chairperson by mutual vote when the Committee chair is not present at a Committee meeting.

(Duties)

Article 6 With respect to the following enumerated matters (see Appendix for specific examples), the duty of the Committee is to receive consultations from the research managers belonging to H.U. Group Companies to conduct reviews and provide opinions.

(1) R&D and clinical tests addressed under Research Ethics Policies and Guidelines.

(2) Studies for introduction or the new introduction for genetic tests.

(3) Other R&D and clinical tests in addition to the preceding paragraph for which consultation regarding ethical consideration is appropriate.

(4) Other matters related to the preceding paragraphs

(Opinion Letters)

Article 7

1. The Committee shall state opinions in writing when approached for consultation as provided in the preceding article.
2. When the Committee states opinions in writing, the Committee shall provide reasons for their conclusions. Members may append their individual opinions to opinion letters.

(Convocation)

Article 8 The Committee chair shall convene meetings of the Committee at least four times per year.

(Quorum)

Article 9 Committee meetings shall be formed when a majority of members are in attendance, attendees consist of both male and female members, and when at least three external members are present. At least one member in attendance must represent each of the aforementioned expert fields (natural science experts, including experts in medicine and medical care, humanities and sociology experts, including experts in ethics and law, and individuals capable of expressing their opinions from a general stance, including the stance of research subjects).

(Deliberations)

Article 10

1. The Committee may request the attendance of persons involved in R&D and clinical tests, seeking explanations or opinions, as necessary.
2. As necessary, the Committee may request documentation and commission the Committee secretariat to conduct investigations.
3. As necessary, the Committee may seek opinions from outside experts.
4. Staff, researchers, and research managers involved in the implementation of R&D as well as staff and division managers involved in clinical tests subject to review shall attend meetings and provide explanations in response to Committee requests. However, said staff,

researchers, or research managers shall not participate in deliberations or decisions of opinion.

(Decisions)

Article 11

1. The Committee shall issue one of four types of opinion: Approval, disapproval, continuous consultation (collegial discussion), or continuous consultation (brief review).
2. The Committee must endeavor to achieve a complete consensus for final opinions. However, opinions may be finalized by a two-thirds consensus when deliberations do not result in a complete consensus. In this case, a summary of the minority opinion shall be appended to the opinion letter.

(Statements of Opinions in Writing)

Article 12 Members who are not able to attend a Committee meeting may provide a statement of their respective opinions to the Committee in writing.

(Expedited Review)

Article 13

1. Reviews corresponding to any of the enumerated matters below that are deemed to be appropriate by the Committee chair may receive an opinion by a review of the Committee chair and members designated by the Committee chair (those members designated by the Committee chair participate in a deliberation only when deemed necessary by the Committee chair) without the Committee chair convening a meeting (Expedited Review).
   (1) Review in case of a joint research where the research in whole has already been independently reviewed by the ethics review committee of the other organization, and such review has provided an opinion that the research in question is appropriate.
   (2) Reviews for minor changes in approved research plans or approved basic studies related to clinical tests, as well as contents of tests already introduced.
   (3) Reviews for non-invasive research that will not involve intervention
   (4) Reviews for minor invasive research that will not involve intervention
2. The Committee chair may convene a Committee meeting any time he or she deems proper, even after the completion of Expedited Review procedures.
3. Results of the Expedited Review shall be treated as the opinion of the Committee. The Committee chair shall promptly report the results of the Expedited Review to all the Committee members.
4. Members receiving reports of Expedited Review results may, after providing justification, seek a new full review within the Ethics Review Committee.

(Expedited Report)

Article 14 In case any of the enumerated matters below should apply, the research manager may change the contents of research without conducting an Expedited Review. Provided however, in case an Expedited Review is not to be conducted on grounds that any of the

enumerated matters below should apply, then the research manager must provide an expedited report to the Ethics Review Committee before or immediately after such change.

(1) When the research period is to be changed.

(2) In case the name of the research organization, the names of divisions and departments, and the job titles are to be changed.

(3) In case the head of the research organization, the research manager and/or the research staff is to be changed.

(4) In case the research staff are to be added or deleted.

(5) In case of making minor corrections or additions to the details of contents are to be made to the approval documents already approved.

(Respect for Ethics Review Results)

Article 15 The research manager shall report the results of review to the head of the research organization, when consultation has been made to the Committee or when a packaged review has been conducted by an ethics review committee of another organization under Article 16, paragraph 2. The head of the research organization shall respect the opinion of the Committee and determine whether to implement it or not. However, projects where the ethics review committees of each organization have given the opinion of disapproval shall not be implemented.

(Packaged Review)

Article 16

1. The research manager may request for a Packaged Review to the Committee in case the research manager is the research representative for the joint research. In this case, required information shall be gathered from each joint research organizations and submitted to the Committee.

2. In the case where the research manager is not the research representative, but when any of the following enumerated matters should apply, the results of packaged review by the external ethics review committee made by the research manager may be used as the ethical judgment regarding the implementation of such joint research in H. U. Group Companies. “Review implementation notification” shall be made prior to submission of materials to the external ethics review committee and “Review results notification” shall be made after the ethical review of by the external ethics review committee to the Committee secretariat.

(1) In case Packaged Review is conducted by an ethics review committee of national and public or domestic private universities and their hospitals.

(2) When Packaged Review is conducted by an ethics review committee that is considered to be able to confirm its ethical safety, similar to (1) above.

(Joint Research Not Utilizing Packaged Review)

Article 17 In case Packaged Review of Article 16 is not to be used, but the subject of review is a joint research, then the research manager shall acquire the opinions and other information of the ethics review committees of the other parties to the joint research and provide it to the Committee.

(Reporting of Deviations and Occurrence of Adverse Effects)

Article 18

1. As a general rule, the research manager shall report the progress of research and deviations and occurrence of adverse effects accompanying the execution of research to the ethics review committee and the head of the research organization, once every year. However, in case of serious deviations or occurrence of grave adverse effects, the research manager shall immediately report the status to the head of the research organization and the ethics review committee and take appropriate action through the sharing of information among the researchers involved in the implementation of the subject research. In addition to the above, in case of occurrence of grave adverse effects, a report shall be made to the status of response and its results to the Minister of Health, Labour and Welfare as well as making it public.
2. In case any of the enumerated matters below should apply. the research manager shall report such to the head of the research organization, and the head of the research organization may request opinion of the ethics review committee, as necessary.
   (1) In case facts that damage or may damage the ethical validity or scientific rationality of the research became known or such information has been acquired, where it is considered that it will impact the continuation of the research.
   (2) When facts that may damage the appropriateness of implementing the research or the reliability of the research results became known or when such information has been acquired.
   (3) When there has been a grave concern from the viewpoint of respecting the human rights of the subjects of research, such as leak of information concerning the research or from the viewpoint regarding the implementation of the research.

(Custody of Samples, Information, and Records)

Article 19

1. Manuals regarding the custody of samples and information obtained from human bodies shall be prepared at each organization and the samples and information acquired from human body must be preserved in an appropriate manner in accordance with the manual.
2. Management of the research plan shall be conducted by the research manager. The period of storage shall be five (5) years from the date of the research completion report submitted to the Committee.
3. The storage period of the minutes of the Committee and related materials shall be for five (5) years from the Committee approval date.

(Ethics Review Committee Reporting System)

Article 20 When initiating the Committee, the Committee Organizer shall publish a list of committee members and rules related to the organization and operations of the Committee in the Ethics Review Committee reporting system, as well as providing at least one summary of meetings and reviews of the Ethics Review Committee in the system on an annual basis. Notwithstanding the preceding sentence, such shall not be required for information stemming from reviews judged by the Committee to require non-disclosure for the protection of the human rights of research subjects or other related persons, or for the protection of the interests of the researchers or other related persons.

(Research Completion Report)

Article 21 The research manager must report the fact of the completion of the research (including the case where it has been terminated), as well as a summary of the research results to the ethics review committee and the head of the research organization.

(Protection of Personal Information and Confidentiality)

Article 22

1. Necessary measures must be taken at each research organization, when handling personal information, not to let any information concerning the research subjects to leak and the structure and rules required for safety management must be organized.
2. Committee members and persons involved in the Committee administration shall not divulge any information obtained through conducting their duties to others, without proper cause. This rule shall remain in effect even after the individual's involvement in the review process has ended.

(Education)

Article 23

1. Ethics review committee members and persons involved in the Committee administration must attend education and training to acquire knowledge required to conduct the review from ethical and scientific point of view, prior to becoming engaged in review and related operations. Furthermore, they must continue to receive education and training continuously thereafter.
2. Prior to the implementation of the research, staff, researchers, and research managers involved in the implementation of R&D, and the staff and division manager in clinical tests must receive education and training concerning ethics and knowledge and skills required to implement the subject research. They must also continue to receive education and training continuously during the research period.

(Secretariat)

Article 24

1. The secretariat for the Committee shall be established at R&D Planning and Promotion Dept., R&D General HQ.The Secretariat shall support the preparation of ethics review application, gathering of information, and the checking of ethics review applications, etc., prior to application, and shall safekeep the materials, and perform other duties.
2. The head of the R&D General HQ shall appoint the head of the Secretarial.

(Revisions)

Article 25 R&D Planning and Promotion Dept., shall be in charge of these guidelines. Revisions and abolition of these guidelines shall be originated by R&D Planning and Promotion Dept., and approved by the Executive Office in charge of R&D.

Supplementary Provisions
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(Appendix)

Matters to Be Reviewed by the Committee

The following provides specific examples of matters to be reviewed by the Committee as set forth in Article 6, Items 1 through 3. Guidelines, etc. on which the matters should be based are specified in the parentheses:

1. Medical and health research involving human subjects (including samples and information), and human genome and gene analysis research (Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Economy, Trade and Industry)
2. Genetic testing (Ethical Guidelines for Genetic Testing Service issued by Japan Registered Clinical Laboratories Association, Guidelines for Implementation of Genetic Tests issued by Japan Pediatric Society, Japanese Society of Neurology, Japan Society of Human Genetics and Japan Registered Clinical Laboratories Association, and Guidelines for Protection of Personal Information in Economic and Industrial Areas Using Personal Genetic Information issued by the Ministry of Economy, Trade and Industry, Guidelines for Genetic Tests and Diagnoses in Medical Practice issued by the Japanese Association of Medical Sciences); and
3. In addition to the preceding items, research for which consultation with the Committee is required by laws and regulations, ethics guidelines for research, guidelines, etc., and clinical tests, research and related matters for which consultation with the Committee is appropriate.