Kyushu University

Standard Operating Procedure for SAE Reporting in Medical and Biological Research Involving Human Subjects

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Chapter 1 General Provisions

No. 1 Purpose and Scope of Application

The purpose of this manual is to ensure the proper implementation of research based on the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (2021 Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; and Ministry of Economy, Trade and Industry Notification No. 1) (hereafter, "the Guidelines") and the "Kyushu University Regulations for Medical and Biological Research Involving Human Subjects" (2021 Kyushu University Regulations No. 48) and, towards that end, prescribes the procedures for dealing with severe adverse events as well as the procedures stipulated in the "Standard Operating Procedures for Medical and Biological Research Involving Human Subjects" (hereafter, "Medical and Biological Research Manual").

Please note, however, that in the case of research for which other laws, regulations, etc., apply, these shall take precedence over this manual.

Also, notwithstanding the stipulations of this manual, in the event of an incident relating to hospital medical safety, a prescribed report shall be made via the "Reporting System for Impact Classification Level 3b or Higher" and in accordance with the separately established "Kyushu University Hospital Basic Policies on Medical Safety Management" and the "Kyushu University Hospital Medical Safety Management Manual."

No. 2 Definition of Terms

The following is the definition of terms used in this manual.

(1) Medical and biological research involving human subjects

This refers to research performed at the Medical Institutions which uses humans as subjects and is conducted for the purpose of a. or b. below (hereafter, "Research").

a. To obtain knowledge, via 1), 2), 3) or 4) below, which will contribute to citizens' health preservation and promotion, patient recovery from injury or illness, or quality of life improvement.
   1) Understand the etiology of injury or illness (including the frequency and distribution of various health-related phenomena and the factors affecting them)
   2) Understand pathology
   3) Verify improvement in, or effectiveness of, injury and illness prevention methods
   4) Verify improvement in, or effectiveness of, medical diagnostic and treatment methods

b. To obtain knowledge, via human-derived samples or data, about human genome and gene structure or function, or about genetic mutation or expression.

(2) Invasive procedure

This refers to any procedure which creates a physical or psychological injury or burden for the research subject as a result of punctures, incisions, drug administration, irradiation, psychologically traumatizing questioning, etc., conducted for research purposes or for purposes beyond those of normal diagnosis and treatment.

Invasive procedures which create minimal physical or psychological injury or burden for research subjects are referred to as "minimally invasive procedures."

(3) Intervention

This refers to any activity performed for research purposes (including any medical activity which goes beyond the scope of normal diagnosis and treatment and which is conducted for research purposes) to control the presence or absence, or degree thereof, of factors (including health preservation or promotion-related activities and medical drug administration, examination, etc., performed to prevent, diagnose or treat injury or illness) which affect various human health-related phenomena.

(4) Sample/information

This refers to human body-derived samples and information used for research, including those derived from the deceased.

a. Human body-derived samples refer to anything taken from a human body, such as blood, fluid, tissue, cells and waste products, or the DNA taken from them, which is used for research purposes.

b. Information used for research refers to any human health-related information or other information obtained from medical examination or treatment of research subjects, such as names of illnesses, content of drug administration, results of examinations or measurements, etc., which is used for research.

c. Existing samples/information refers to samples/information for which either of the following criteria apply.

   1) Any sample/information which already exists prior to research plan creation

   2) Any sample/information obtained after research plan creation but, at the time it is obtained, not for the purpose of the research in question

(5) Research subject

This refers to any person (living or deceased) for whom either of the following criteria apply.

1) A person upon whom research is performed (including anyone who has sought to have the research performed)

2) A person from whom existing samples, information, etc., have been obtained and which will be used for research

When referring not only to research subjects but to others associated with them, such as legal representatives, the expression “research subjects and related parties” is used.

(6) Joint research institution

This refers to any institution with which research is carried out jointly and in accordance with a research plan (this includes institutions which obtain new samples/information from research subjects to provide to other research institutions for the purposes of the research in question).

(7) Research affiliate

This refers to an institution, other than one which conducts research in accordance with the research plan, which solely obtains and provides to research institutions new samples/information from research subjects (not including cases where invasive procedures (but not minimally invasive procedures) are used to obtain samples) for the purposes of the research in question.

(8) Multi-institutional joint research

This refers to research which is conducted by multiple research institutions based on a single research plan.

(9) Researchers and related parties

This refers to the principal investigator and others who are involved in conducting the research. However, this does not include anyone who does not belong to a research institution and for whom any of the following apply.

1) Someone whose sole involvement is obtaining new samples/information and providing these to research institutions

2) Someone whose sole involvement is providing existing samples/information

3) Someone who is contracted to perform only some of the research-related tasks

(10) Principal investigator

This refers to the individual who is involved in conducting the research as well as responsible for supervising all tasks connected with the research at Kyushu University. As a rule, the principal investigator must be a Kyushu University staff member.

In cases of multi-institutional joint research, the term “research representative” can be used as an equivalent term for “principal investigator” when necessary.

(11) Research representative

This refers to the principal investigator who is the representative for the principal investigators of multiple research institutions in the case of multi-institutional joint research.

(12) Research director

This refers to the head of the department at Kyushu University which is conducting the research.

(13) Ethical review boards

This refers to boards and committees which have been established to investigate, from an ethical and scientific standpoint, the appropriateness of conducting or continuing research, as well as to review any necessary research-related matters.

(14) Side effects

This refers to adverse events which arise in research subjects participating in research and for which a causal relationship with the interventions or sample collection performed as part of the research is at least reasonably possible or cannot be ruled out.

(15) Nonconformities

This refers to adverse events which arise in research subjects participating in medical instrument-related research and for which the breakage, malfunctioning, etc., of said instrument, regardless of whether it occurs during instrument design, manufacture, sale, delivery, storage or use, broadly and negatively affects the instrument in terms of quality, safety, performance, etc., and a causal relationship between this and the adverse event is at least reasonably possible or cannot be ruled out.

(16) Adverse event

This refers to any undesirable or unintentional injury or illness, or symptom thereof (including abnormal laboratory test values) arising in the research subject, regardless of whether the cause is connected with the research conducted.

(17) Severe adverse event

This refers to an adverse event for which any of the following criteria apply.

1) The adverse event is fatal
2) The adverse event is life-threatening
3) The adverse event requires hospitalization or extension of the hospitalization period to treat
4) The adverse event leads to lasting or pronounced disability or malfunction
5) The adverse event gives rise to heritable congenital abnormalities
6) The adverse event, while not producing the outcomes described in 1) - 5) above itself, exposes the research subject to serious danger or other factors which must be dealt with in order to avoid the outcomes described in 1) - 5) above.

(18) Unforeseeable severe adverse event

This refers to a severe adverse event which is not included in the research plan, informed consent explanatory documents or elsewhere, or which, even if it has been included, has properties or severity different from what was anticipated.

(19) Safety information

This refers to information about severe adverse events occurring at other facilities, increases in the frequency of foreseeable severe adverse events, the ineffectiveness of drugs used to treat life-threatening illnesses, etc., as well as information relating to results or data that suggests serious risks, such as mutagenicity, carcinogenicity, or teratogenicity, to subjects.

Chapter 2 Response of Researchers and Related Parties, Principal Investigators and Research Directors

No. 3 Response of Researchers and Related Parties

(1) In the event that researchers and related parties learn of a severe adverse event or nonconformity occurring in the course of research which involves invasive procedures, they shall take all necessary steps, such as providing an explanation to research subjects and related parties, and shall promptly report the occurrence to the principal investigator.

(2) With regard to reporting cases in which the severe adverse event is suspected to be due to the side effects of medicinal drugs, or nonconformities associated with medical instruments, used in the research, the researchers and related parties shall respond appropriately in accordance with the “Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical

Devices (Act No. 145 of August 10, 1960)."

No. 4 Response of the Principal Investigator

(1) Before attempting research involving invasive procedures, the principal investigator shall describe in the research plan the procedures which researchers and related parties should take in the event of a severe adverse event, and he/she shall take all necessary steps to ensure that the response is proper and executed smoothly in accordance with said procedures.

(2) In the event that the principal investigator asks a research affiliate to obtain research-related samples/information and a severe adverse event occurs for the research subject, the principal investigator shall promptly obtain a report of the matter.

(3) Upon learning of a severe adverse event occurring in the course of research which involves invasive procedures, the principal investigator shall promptly seek the opinion of the relevant ethical review board regarding the event, whether to continue the research, etc., shall make a report to the research director and shall facilitate proper handling of the situation in accordance with this manual. Also, the principal investigator shall promptly share information relating to the occurrence of the adverse event with the researchers and related parties involved with the research in question.

(4) Upon learning of a severe adverse event occurring in the course of research which involves invasive procedures and which is being conducted as multi-institutional joint research, the research representative shall promptly share with the principal investigators of the joint research institutions conducting the research any information relating to the occurrence of the adverse event, as well as implement the handling process stipulated in (3).

(5) In the event that an unforeseeable severe adverse event occurs in the course of research involving interventions and accompanied by invasive procedures (but excluding minimally invasive procedures) and a direct causal relationship with said research cannot be discounted, the principal investigator of the research institution where the adverse event occurred shall, after making a report to the head of the research institution (in the case of the University, the research director), make a report to the university president and the Minister of Health, Labour and Welfare about the status of response conducted in line with the stipulations of (2) and (3), as well as the results, after which the principal investigator shall provide public disclosure.

(6) During the research implementation period, the principal investigator shall, at least once per year, provide an updated "Research Implementation Status Report" which describes the status of research progress and any adverse events and nonconformities which have occurred, and he/she shall then submit this report to the relevant ethical review board and the research director.

No. 5 Response of the Research Director

After receiving a severe adverse event/nonconformity report from the principal investigator, the research director shall, when necessary, consult with the relevant ethical review board and promptly take appropriate action in line with the procedures stipulated in 3., including pausing the research and performing an investigation into the cause. In such cases, prior to receiving the opinion of ethical review boards, the research director shall instruct the principal investigator to take action as needed, including discontinuing the research or implementing provisional measures.

Chapter 3 Reporting Procedures for Severe Adverse Events and Nonconformities

No. 6 Reporting Severe Adverse Events and Nonconformities

(1) Upon receiving a report from researchers and related parties, the principal investigator shall promptly create a "Severe Adverse Event Report (for medical instrument-related reports, "Severe Adverse Event and Nonconformity Report;" hereafter, collectively, "adverse event report") and shall submit it to the relevant ethical review board, as well as provide a copy to the research director. The adverse event report shall be submitted to the administrative processing section (see the appended table) of the ethical review board which reviewed the research in question.

(2) In cases of multi-institutional joint research which has an adverse event report form separately prescribed by the joint research plan, the principal investigator may attach this form to the adverse event report for those areas where the details are overlapping.

However, any matters asked about in the adverse event report which are not asked about in the separately established form must be addressed in the adverse event report submitted.

(3) The principal investigator shall, when the report content involves an incident relating to hospital medical safety, make the report via the "Reporting System for Impact Classification Level 3b or Higher" and in accordance with the "Kyushu University Hospital Basic Policies on Medical Safety Management" and the "Kyushu University Hospital Medical Safety Management Manual."

(4) The relevant ethical review board shall confirm and investigate the content of the adverse event report submitted as per (1) and shall report its opinion to the principal investigator.

(5) The principal investigator shall show due consideration for the ethical review board's opinion, taking all necessary measures, as follows, for the research in question, and shall make a report to the research director.

1) Approval or disapproval of research continuation; revision or alteration of the research plan, consent explanation form, or various manuals, procedures, etc.; take measures relating to reobtaining consent from/providing explanations to subjects; submit supplemental severe adverse event report information.

2) Take steps to raise awareness among, reeducate, etc., researchers and related parties.

3) In the case of multi-institutional joint research, provide a written report of severe adverse events and nonconformities to the joint research institutions.

4) When there is an unforeseeable severe adverse event, and when the research in question cannot be ruled out as a direct cause, submit the necessary reports, information etc., in line with No. 7.

5) Take other, essential measures.

(6) If, after submitting the first adverse event report, new, additional information is obtained which should be reported, the principal investigator shall create and submit an additional report according to the same process used for the first report.

No. 7 Report to the Minister of Health, Labour and Welfare about Unforeseeable Severe Adverse Events

(1) In the event that an unforeseeable severe adverse event occurs in the course of research involving interventions and accompanied by invasive procedures (but excluding minimally invasive procedures), and a direct causal relationship with said research cannot be discounted, the principal investigator shall, after making a report to the research director, make a report to the university president and the Minister of Health, Labour and Welfare in line with the stipulations of the Guidelines.

(2) When the scope of application of the research encompasses other laws, regulations, guidelines, etc., the principal investigator shall make reports to the relevant authorities in line with the stipulations of said laws, regulations, guidelines, etc.

(3) If a report has been made to the Minister of Health, Labour and Welfare as per (1), the principal investigator shall publicly disclose the status of response, as well as results, for the adverse event, according to the content of the event, via conference, publication on the homepage and/or some other method.

No. 8 Reporting Severe Adverse Events and Nonconformities Occurring at Other Joint Research Institutions

(1) When a principal investigator obtains information about a severe adverse event or nonconformity occurring in the course of multi-institutional joint research at another joint research institution or research affiliate, he/she shall follow the same procedure stipulated in No. 6.

(2) When there is an unknown severe adverse event, and when the research in question cannot be ruled out as a direct cause, the report to the Minister of Health, Labour and Welfare shall be handled by the research representative working in conjunction with the institution where the severe adverse event or nonconformity occurred.

No. 9 Managing Information for Reporting Severe Adverse Events and Nonconformities

(1) With regard to severe adverse event and nonconformity reports, the administrative processing section stipulated in No. 6(1) shall collect and manage information about whether or not reports were made to the Minister of Health, Labour and Welfare and, if they were, information about their content and its handling.

(2) When a severe adverse event or nonconformity report includes content about an incident relating to hospital medical safety at Kyushu University Hospital, the Kyushu University Hospital Medical Safety Management Department shall collect and manage the information in accordance with the separately established "Kyushu University Hospital Basic Policies on Medical Safety Management" and the "Kyushu University Hospital Medical Safety Management Manual."

(3) The Safety Information Management Office of the ARO Next-Generation Medical Center will regularly check the information described in (1) and (2) in order to confirm whether or not reporting of severe adverse events and nonconformities occurring at Kyushu University Hospital is being performed appropriately.

No. 10 Collecting, Reporting and Addressing Safety Information

(1) With regard to interventions and sampling collection methods implemented in the course of research, the principal investigator shall endeavor to collect and study the content of research presentations given in Japan or overseas, as well as information about safety measures implemented by regulatory authorities in Japan or overseas.

(2) The principal investigator shall, upon obtaining significant, new information which could adversely impact research subject safety or research implementation, seek the opinion of the relevant ethical review board before promptly submitting said information in writing to the research director as well as altering the research plan as necessary.

(3) Research representatives shall promptly share such information with the principal investigators at joint research institutions.

Supplementary Provisions

1. All revisions to this manual must be approved by the Kyushu University Medical Ethics Council.
2. This manual shall come into effect from June 30, 2021.

Attached Table

Ethical review boards	Administrative processing section
Kyushu University Institutional Review Board for Clinical Research	Administrative Office, Academic Research Cooperation Division, Bioethics Section TEL: 092-642-6772 (ext.: 6772) e-mail: ijkseimei@jimu.kyushu-u.ac.jp
Kyushu University Institutional Review Board for Human Embryonic Stem Cells Derivation and Utilization Research	
Kyushu University Institutional Review Board for Clinical Trials	University Hospital Administration Department Research Support Division, Section of IRB & Ethics Committee Administration TEL: 092-642-5082 (ext.: 5082) e-mail: byskenkyui@jimu.kyushu-u.ac.jp
Kyushu University Certified Special Committee for Regenerative Medicine	