Form 1 (Common－1)

Ethical Review Application Form

To: Dean, Mie University Graduate School of Medicine
Director, Mie University Hospital August 21, 2013

Name of Principal Investigator (applicant): Hajime Sakuma Seal
Affiliation: Department of Radiology, Division of Clinical Medical Science, Graduate School of Medicine, Mie University
Official title: Professor

＊Receipt number: №
＊Date of receipt: year month day

Department head: Hajime Sakuma Seal:

Applicable ethical guidelines (please circle)	(1) Ethical guidelines for epidemiologic studies (2) Ethical guidelines for clinical studies (interventional or observational) (choose one) (3) Ethical guidelines for clinical studies of human stem cells (4) Ethical guidelines for research on the human genome and genetic analysis (newly procured specimens or previously procured specimens) (choose either one) Note: As for applications for clinical studies of gene therapy or other types of treatment, inquires should be made to the "Gene Therapy Clinical Research Deliberation Committee" or the "Therapy Quality/Ethics Review Committee."
Submission of documents regarding conflict of interest	Yes or No (Put circle either one at the administrative office in charge)

The presence or absence of participation in clinical study ethics training sessions: (Yes) (April 13, 2009) For clinical studies, training is mandatory.

1 Research title: Asia CMR Registry – A Registry Study of Cardiac MRI in Asia

2 Study organization

(1) Principal Investigator (applicant) Name, affiliation, title

Prof. Hajime Sakuma, Department of Radiology, Division of Clinical Medicine Research, Graduate School of Medicine, Mie University

Director in charge of the Multi-Centre Research Committee, Asian Society of Cardiovascular Imaging,

(2) Person in charge of the study Name, affiliation, title

Representative of institution participating in this study in Asia as approved by the Multi-Centre Research Committee of the Asian Society of Cardiovascular Imaging (ASCI)

3 Multicenter study (If applicable, attach the study protocol.)

Joint research theme: Asia CMR Registry – A Registry Study of Cardiac MRI in Asia

Research representative: Name [Hajime Sakuma], affiliation [Department of Radiology, Division of Clinical Medicine, Mie University Graduate School of Medicine]

Address: [2-174 Edobashi, Tsu-shi, Mie 514-8507, Japan]

Telephone: [059-231-5029], FAX: [059-232-8066]

Approval by an ethics committee, etc. in the institution of the research representative or related committees in affiliated hospitals (① Done ② Under application ③ Not yet done)

Differences between the joint study protocol and present study protocol (① Absent (→ abbreviated review) ② Present (→conventional review)

List of attached documents: study protocol, investigator's brochure,** informed consent explanation form (presence or absence of compensation insurance), informed consent from all subjects

Note: *Do not fill in. Submit only required documents. **For approved pharmaceuticals, the package insert can be submitted as the investigator's brochure.

4 Concept of the study (; the contents of the study should be generally understood after reading this page.)

Background (the reason why this study was designed)

Cardiac MRI is a noninvasive imaging technique for the diagnosis of cardiac disease, without

exposure to radiation. Cardiac MRI in combination with other imaging techniques can provide various types of information on the morphology, function, and volume of the heart; the diagnosis of myocardial ischemia; the evaluation of myocardial infarction and fibrosis; and coronary stenosis. The examination cost is less than that of radionuclide studies. Therefore, cardiac MRI is considered very useful for the diagnosis of coronary artery disease and myocardial disease. In Japan and Asia, however, the current usage and safety of cardiac MRI, its role in deciding the treatment policy, and its usefulness for the evaluation of prognosis remain unclear. In Europe, the European Society of Cardiac Magnetic Resonance started the EuroCMR Registry, "a multicenter registry study of cardiac MRI in Europe," in 2007. To date, several tens of thousands of cardiac MRI case data and images have been compiled. Studies on the status of the clinical use of cardiac MRI, examination safety, the role of cardiac MRI in determining treatment policy, and the usefulness of cardiac MRI for the evaluation of prognosis are ongoing. However, the cardiac disease incidence and healthcare systems differ between Europeans and Asians. Studies on the current usage, safety, and effectiveness of cardiac MRI in Asians, including Japanese, have therefore become more important.

Objective (What will be clarified within the specified period?)

The objective of the present study is to clarify the current usage and safety of cardiac MRI in Asia, the image quality of cardiac MRI, the role of cardiac MRI in the treatment of cardiac disease, and the usefulness of cardiac MRI for the evaluation of prognosis. The study will be mainly conducted by the Asian Society of Cardiovascular Imaging (ASCI). A server will be established in Mie University, the core institution, and case data on cardiac MRI and MR images will be compiled. This is a registry study performed in cooperation with the EuroCMR Registry. The methods for compiling clinical data and images on cardiac MRI will be in accordance with the EuroCMR Registry.

Subjects and Methods

The study group will comprise patients who undergo cardiac MRI for diagnosis and treatment in medical institutions participating in the Asia CMR Registry and give informed consent to the registration of anonymous data. Patient characteristics and information concerning the performance of cardiac MRI will be made completely anonymous and encrypted and will then be registered in a Web-based registry system via a server. In addition, DICOM images of cardiac MRI examinations will be made completely anonymous and uploaded to a dedicated server. Follow-up surveys will be performed at 12-month intervals after cardiac MRI examination to confirm outcomes such as overall mortality and cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, acute

coronary syndrome, revascularization, heart failure, hospitalization for arrhythmias, cerebral infarction, peripheral vascular lesions, ICD shock).

Predicted results and academic significance

In Asia, a prospective multicenter registry study of cardiac MRI has yet to be performed. The results of the present study are expected to demonstrate the current usage status and safety of cardiac MRI in routine medical practice in Asia, the significance with regard to the treatment policy for cardiac disease, and the significance for the evaluation of prognosis and risk stratification for various cardiac diseases, thereby establishing the clinical usefulness of cardiac MRI examinations.

Possible ethical problems and countermeasures

In this study, personal information on patients who undergo cardiac MRI for diagnosis and treatment will be registered in a Website, and DICOM images of cardiac MRI examinations are uploaded to a dedicated server. These information and data, including the DICOM header, are made completely anonymous, and a high-level encryption system will be used at the time of Web input and image uploading to prevent the leakage of patients' personal information to third parties.

5 Study protocol

(1) Study period: from the date of approval until September 30, 2023

(2) Main study site:

Mie University Hospital (site of server)

Participating institutions in this study approved by the Multi-Centre Study Committee of the Asian Society of Cardiovascular Imaging (ASCI)

Institutions scheduled to participate and names of investigators (as of June 1, 2014)

Tokyo Medical University Hachioji Medical Center (Kunihiko Teraoka), Saitama International Medical Centre (Fumiko Kimura), Hyogo Brain and Heart Center (Yasuyo Taniguchi), Nippon University Itabashi Hospital (Satoshi Kunimoto), Aoyama Hospital Tokyo Women's Medical University (Eri Watanabe), Keio University Hospital (Shigeo Okuda), Kanagawa Cardiovascuiar and Respiratory Center (Tae Iwasawa), Saitama Prefectural Cardiovascular and Respiratory Disease Center (Takatomo Nakajima), Toyama City Hospital (Hiroaki Kiyokawa), Juntendo University Hospital (Eiryu Sai), Seoul National University Hospital (W Lee), and Seoul National

University Bundang Hospital (YE Yoon), etc.

(3) Details of subjects (characteristics, number of patients, and others)

The study group will comprise patients who undergo cardiac MRI for diagnosis and treatment in hospitals participating in the Asia CMR Registry and give informed consent to the registration of anonymous data. For persons willing to cooperate in the study who are younger than 20 years, informed consent will be obtained in accordance with criteria previously defined by each country or each participating medical institution. In Mie University Hospital, consent from a legal guardian must be obtained for persons willing to cooperative in the study who are younger than 20 years. If persons willing to cooperate in the study are younger than 20 years but 16 years or older, consent must be obtained directly from the subject as well as from a legal guardian.

(4) Concrete study protocol (if the study extends over multiple years, fill in according to year)

Enrollment started in 2013

Patient enrollment and cardiac MRI examinations

Among cardiac MRI examinations performed at medical institutions participating in the Asia CMR Registry, patient information such as the purpose for requesting cardiac MRI examinations and the examination methods will be made completely anonymous and encrypted and then be registered in a Web-based registry system. In addition, DICOM images of cardiac MRI examinations will be made completely anonymous and encrypted and then be uploaded to a dedicated server. Compiled data will be managed in accordance with the EuroCMR Registry. Personal information that has been made completely anonymous and encrypted will be provided to core institutions approved by the Multi-Centre Study Committee, Asian Society of Cardiovascular Imaging (ASCI), where it will be studied to examine factors such as the purpose for requesting cardiac MRI examinations, the safety of loading tests and contrast radiography, the image quality of cardiac MRI, and the role of cardiac MRI in determining the treatment strategy.

Outcome survey

Outcomes will be surveyed at 12-month intervals after cardiac MRI examinations. Overall mortality and the presence or absence of cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, revascularization, heart failure, hospitalization for arrhythmias, cerebral infarction, peripheral vascular lesions, and ICD shock) will be followed up. For follow-up, the study staff will interview patients in the outpatient clinic, review patients' outpatient or inpatient records, directly contact patients or their relatives by telephone, or ask patients' current

physicians at 12-month intervals after the examination to collect information. After the information has been collected, statistical analysis will be performed to evaluate the effectiveness of cardiac MRI for predicting outcomes.

Minimal patient follow-up duration is 12 months. Therefore, the patient registration and follow-up period is from the date of approval until September 30, 2022 and September 30, 2023, respectively.

When the patient number will successfully reach 10,000 before September 30, 2022, patient recruit will be continued until September 30, 2022. When the patients number will not reach 10,000 as of September 30, 2022, Multi-Centre Study Committee of the ASCI will be held and discuss if the study period is extended or not.

Interim analysis will be performed every 3 years from the date of approval. Then, "interim analysis report" will be documented as soon as possible. Within 6 months after completion of the study period, September 30, 2023, "Research result report" will be documented. Those results will be considered to go for the publication in English peer-reviewed medical journals.

(5) Possibility of future revisions of, and additions to, subjects and methods

Because registered data items are in accordance with the EuroCMR, any additions to the EuroCMR registered data items will be handled appropriately in accordance with the EuroCMR.

If any additions or revisions of the medical institutions participating in this study are made, the changes will be reported by submitting a "Study Protocol Revision Form" every year.

(6) Rationale why the study must be performed in human subjects to achieve its objectives

This is a multicenter registry study of patients who undergo cardiac MRI for diagnosis and treatment, and non-human subjects cannot be used.

(7) Source of research funds (Representative/co-researchers) (Please write clearly and concretely because of the relation to conflict of interest.)

Grants - in - aid for Scientific Research [item:]

Other government agencies: [ ]

Contract research・joint study [ ]

(Others) [ ]

6 Main ethical problems that should be considered in this study

(Circle the applicable number. If 4 is selected, fill in [ ].)

① The possibility of exposing persons cooperating in the study to physical stress, invasiveness, and other risks

② The possibility that the results of the study for the individual may create substantial, unexpected mental stress for persons cooperating in the study

③ The possibility that leakage of personal information may cause considerable mental and social disadvantages for persons cooperating in the study

4 The possibility of other ethical problems occurring [ ]

(Note)

1 Fill in or circle the applicable items.

2 For 1 to 6, fill in similarly for all application purposes.

3 For the following items, use appropriate forms according to the "applicable ethical guidelines."

7 Consideration and handling of ethical problems potentially caused by this study

(1) Are the following principles included in the ethical review application form and the explanation form for persons cooperating in the study? (Circle the applicable number.)

① This study is conducted with the voluntary consent and cooperation of persons cooperating in the study. Consent can be withdrawn at any stage, and the desired type of treatment can be selected. Moreover, no disadvantages will be caused by refusal.

② All cooperation with the study is done on the basis of fully informed consent (see below).

③ Efforts should be made and measures taken to maximally reduce or avoid mental and physical stress health, invasion, and risks.

④ Maximum care and countermeasures should be taken to avoid mental and social disadvantages to persons cooperating in the study caused by personal information and leakage of personal information.

(2) Prediction of mental stress, invasion, and other risks and countermeasures to reduce such risks

① Stress

In this study, patients who undergo cardiac MRI for diagnosis and treatment will be registered in a registry. Mental stress associated with entering an MR unit and stress associated with the use of intravenous MR contrast media and other agents (ATP) are similar to stress associated with cardiac MRI examinations performed for diagnosis and treatment. The participating institutions will be informed in advance to put technicians and physicians well experienced in cardiac MRI in charge of the examinations to reduce the anxiety of patients at the time of examination.

② Invasion

An intravenous route should be established via the cubital vein to allow the administration of contrast media and coronary vasodilators; invasiveness is similar to that of conventional cardiac MRI examinations. The participating medical institutions will be informed in advance to make efforts to reduce invasion by having experienced physicians perform examinations using a fine venous indwelling needle.

③ Other risks

No particular other risks have been recognized.

(3) Advantages and disadvantages for persons cooperating in the study

① Advantages

If this study demonstrates that cardiac MRI is effective for risk stratification and prognosis in patients with cardiac disease, it may contribute to the selection of more appropriate treatment and prophylaxis for the participants.

② Disadvantages

The present study requires registration of MRI examinations performed for diagnosis and treatment in a registry. MRI is a noninvasive examination technique unaccompanied by exposure to radiation, but is associated with the risk of adverse effects caused by contrast agents and administered drugs, similar to conventional cardiac MRI examinations. If MRI examinations for diagnosis and treatment may possibly be registered in a registry, each participating institution will be informed about the need to obtain written informed consent after providing an explanation of the risk of adverse effects caused by contrast agents and administered drugs. The explanation will be provided by using an examination informed consent form.

(4) Disclosure of the results to persons cooperating in the study (yes / no)

① Reasons for disclosure or nondisclosure

The results will be disclosed because there is no particular reason for nondisclosure.

② Persons to be informed of the results in the event of disclosure

Persons cooperating in the study/their relatives if approved and requested by the person

③ Methods for disclosure

In principle, the attending physician will orally disclose the results to the person concerned.

(5) Protection of personal information of persons cooperating in the study: Circle the applicable item number, symbol, or choice, or write a short comment in parentheses. Confirm whether or not all of the items are included in the study protocol and written informed consent form.

5-1) Protection of personal information in the Asia CMR Registry server located in Mie University

Registered and stored patient data and cardiac MRI image data that are received from each participating medical institution and stored in the patient data server and DICOM image server managed by Mie University, the core institution of this study, will all be made completely anonymous and encrypted. No personal information including patient ID numbers will be included.

① Informed consent (explanation and consent) will be obtained in writing (explanatory documents and the informed consent form are attached) (**see previous page**).

② Handling of personal information on persons cooperating in the study

a. Linkable and saved (personal information corresponding to specimens and materials)

b. Linkable and not saved (Non-linkable and saved data and personal information will be discarded after the collection of data and specimens.)

c. Personal information is not collected.

Total pieces of personal information (number of persons) (including scheduled): [ ]

If linkable data are saved:

Name of person responsible for managing personal information: [ ]

Contact address: [ ]

Storage form of personal information: (documents / electronic information)

Adding linkable saved data to data from other institutions (joint research) (may occur / may not occur)*.

*In the case of "may occur":

1) Specimens and materials are provided to other institutions after being made anonymous.

2) Specimens and materials are provided to other institutions without being made anonymous. (Note: Informed consent from the person is extremely important.)

③ Handling of personal information after completion of the study

a. Stored as linkable data without modification. The scheduled storage period is until (year) [ ] month [ ].

b. Immediately discarded

④ Storage and handling of specimens and materials other than personal information*

The contents and numbers of specimens and materials (summary) [10,000 anonymous DICOM image files in all participating institutions]

Storage place: [Department of Radiology, Mie University Hospital]

Person responsible for storage: [Ryohei Nakayama]

Contact address: [Department of Radiology, Mie University Hospital]

*If provided to other institutions, ① the name of the institution and ② the consent form of the institution (prohibition of use other than for the intended purpose, management of personal information, etc.) is to be attached as an appendix.

a. For a study of linkable data, data will be stored only for the same period as that in 3-a and then immediately discarded.

b. For a study of linkable data, data are made anonymous and stored even after the linkable storage period described in 3-a. Or, originally non-linkable data are stored.

1) The scheduled preservation period is until year [ ] month [ ], after which the data will be immediately discarded.

2) Stored indefinitely.

c. Others: Anonymous data and DICOM files including no personal information will be stored until September 2033.

⑤ Public announcement of the study results

ⓐ. The results of the study will be publically announced at medical congresses or in journals in a completely anonymous fashion.

ⓑ. The data will be stored even after the completion of the study period and used for scientific research under the condition of anonymity.

5-2) Protection of personal information at medical institutions participating in the Asia CMR Registry

At each participating medical institution, unique 64-digit registration numbers are automatically and randomly assigned as patient IDs at the time of registration in the Registry server. However, because these numbers are not transferred to or stored in the Registry server, a list linking the patient ID with the Registry server registration numbers will be prepared at each participating medical institution, and the person responsible for the management of personal information will be informed to preserve the list in the hospital. No other linkage lists will be prepared.

In Mie University Hospital, only a list linking the IDs of patients in Mie University Hospital with the Registry server registration numbers will be preserved in the hospital by the person responsible for the management of personal information.

① Informed consent (explanation and consent) will be obtained in writing (explanatory documents and informed consent form are attached).

② Handling of personal information on persons cooperating in the study

a. Linkable and saved (personal information corresponding to specimens and materials)

b. Linkable and not saved (Non-linkable and saved data and personal information is discarded after the collection of data and specimens.)

c. Personal information is not collected.

Total pieces of personal information (number of persons) (including scheduled): ［2000］

If linkable data are saved:

Name of person responsible for managing personal information: ［Takahiro Takada］

Contact address: ［IT Information Center of School of Medicine］

Storage form of personal information: (documents / electronic information)

Adding linkable saved data to data from other institutions (joint research) (may occur / may not occur)*.

*In the case of “may occur”:

1) Specimens and materials are provided to other institutions after being made anonymous.

2) Specimens and materials are provided to other institutions without being made anonymous. (Note: Informed consent from the person is extremely important.)

③ Handling of personal information after completion of the study

a. Stored as linkable data without modification. The scheduled storage period is until (year) [2033] month [September].

If the person responsible for personal information is changed, the study ethics committee is to be promptly notified, and the change is to be reviewed.

b. Immediately discarded

④ Storage and handling of specimens and materials other than personal information*

The contents and numbers of specimens and materials (summary) ［2000 anonymous DICOM image files in Mie University Hospital］

Storage place: [Department of Radiology, Mie University Hospital]

Person responsible for storage: [Ryohei Nakayama]

Contact address: [Department of Radiology, Mie University Hospital]

*If provided to other institutions, ① the name of the institution and ② the consent form of the institution (prohibition of use other than for the intended purpose, management of personal information, etc.) is to be attached as an appendix.

a. As a study of linkable data, data will be stored only for the same period as that in 3-a and then immediately discarded.

b. The study involves linkable data, but data are made anonymous and stored even after linkable storage period described in 3-a. Or, originally non-linkable data are stored.

1) The scheduled preservation period is until month [ ] year [ ], after which the data will be immediately discarded.
2) Stored indefinitely.

c. Others

⑤ Public announcement of the study results

ⓐ. The results of the study will be publically announced at medical congresses or in journals in a completely anonymous fashion.

ⓑ. The data will be stored even after the completion of the study period and used for scientific research under the condition of anonymity.

(6) Methods for legal representation for persons cooperating in the study who are unable to give consent (because of death, loss of consciousness, etc.) or persons with intellectual or mental disabilities, persons younger than 20 years, and others who are suspected to be incapable of giving informed consent: not applicable

(7) All of the above items (1) to (6) are (included / not included) in the explanation or informed consent form (**see previous page**).

(8) Concern about other ethical problems

None

8 If the study is conducted using existing samples, etc. (biologic samples, health-related information, etc.) or existing personal information

(1) Specimens obtained from humans health-related information existing personal information others:

(2) Quantity (number of persons [ ] Quantity of samples, etc. per person [ ])

Other details:

(3) Consent for the use in this study yes no (see below)

(4) Name of the institution or bank storing the specimens, etc. [ ]

(5) Name affiliation, and title of person responsible for management of specimens

[ ]

(6) Name of ethics committee that reviewed the study protocol

[ ]

(7) Approved preservation period

[Approval date: year month day to year month day]

(8) Storage form (linkable storage / non-linkable storage / bank)

(9) Method to access specimens, etc.:

Important item: If informed consent was not obtained directly from the person or from a legal representative for 7-(1) or 8-(3), the necessity, rationale, and action taken in accordance with the applicable ethical guidelines should be attached as an appendix.