—Special Report—

Nippon Medical School's Ethical Review Processes for Studies Involving Human Subjects

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All life science and medical research involving human subjects must be conducted in compliance with the Declaration of Helsinki and the relevant laws and guidelines. Additionally, its scientific and ethical suitability must be reviewed by a committee well versed in the nature and content of the research. Failure to comply with these requirements when conducting research involving human subjects is a serious violation of Japanese laws, guidelines, and local regulations, so several ethics committees and institutional review boards have been established within the Nippon Medical School (NMS) Foundation and its affiliated institutions. It is essential for investigators to keep up to date with the latest developments in the ethical review process and to ensure that any projects they propose to embark on are subjected to an appropriate ethical review before the research is initiated. To help researchers and other staff affiliated with the NMS Foundation keep abreast of these developments, this report outlines NMS's current ethical review processes for research involving human subjects.
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Key words: ethical guidelines, ethics committees, research subjects, specified clinical trials

All life sciences and medical research involving human subjects must be conducted in compliance with the Declaration of Helsinki[1], and in Japan, such research also has to be in accordance with the relevant laws and guidelines pertaining to the content and objectives of the research. Registered clinical trials aimed at securing regulatory approval of new drugs, for example, must be conducted in accordance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices[2] and the Ministerial Ordinance on Standards for Conducting Clinical Trials on Pharmaceuticals[3], whereas clinical research on regenerative medicine has to follow the regulations laid out in the Act on Securing Safety of Regenerative Medicine[4], and specified clinical trials (SCTs) are governed by the Clinical Research Act[5]; other medical and life science research on human subjects are subject to the Ethical Guidelines for Life Science, Medical and Health Research Involving Human Subjects[6].

Regardless of which laws or guidelines are applicable to a specific research project, its scientific and ethical suitability must be reviewed by a committee well versed in the nature and content of the research. Several ethics committees and institutional review boards (IRBs) have been established for this purpose by the Nippon Medical School (NMS) Foundation and its affiliated institutions (**Fig. 1**). The Central Ethics Committee and Certified Institutional Review Board (CRB) were established by the NMS Foundation, while other ethics committees and IRBs were set up by NMS and its affiliated hospitals (NMS hospitals). Registered clinical trials and ancillary research carried out at NMS hospitals are subject to review by the relevant hospital's IRB, although it is also possible to have reviews performed by external IRBs certified by the NMS Foundation. SCTs and clinical research

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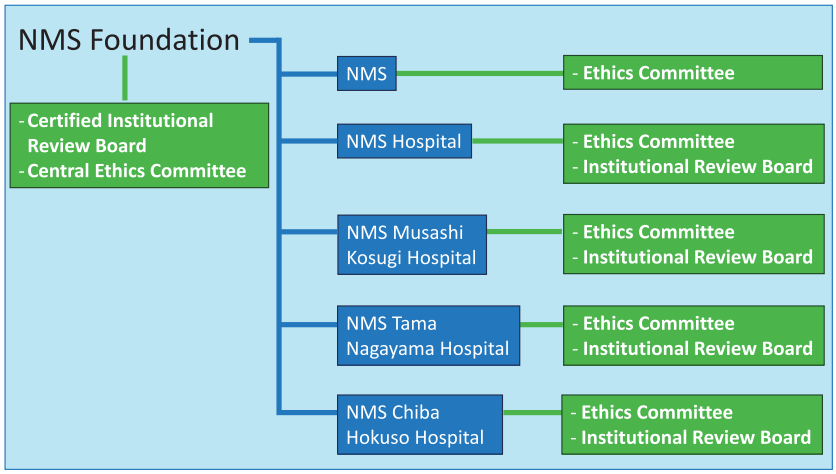

Fig. 1 Ethics committees and institutional review boards established within NMS Foundation and affiliated institutions.
NMS: Nippon Medical School

in regenerative medicine are subject to review by the CRB and the Certified or Specially Certified Committee for Regenerative Medicine, respectively, which are certified by the Ministry of Health, Labour and Welfare. Under the Clinical Trials Act and the Act on the Safety of Regenerative Medicine, there is no requirement for reviews to be conducted exclusively by committees established within the same institution as the research is scheduled to be conducted. However, in the case of a single-center SCT conducted at an NMS hospital or a multicenter SCT with an NMS hospital serving as the representative institution, a review by an NMS Foundation committee is recommended. The Clinical Trials Act requires that a single CRB perform the review of a multicenter SCT, which is known as a batch review. Therefore, if a batch review of a multicenter SCT involving an NMS hospital has been carried out by an external CRB, there is no need for it to be re-reviewed by the NMS Foundation's CRB.

Excluding registered clinical trials, SCTs, and clinical research for regenerative medicine, all life science and medical research involving human subjects must be reviewed by the NMS Foundation's internal or external ethics committees in accordance with the current ethical guidelines; the type of research determines which ethics committee is assigned to carry out the ethical evaluation. When applications are submitted for approval of, for example, revised study protocols for research projects already approved by NMS or NMS hospital committees under previous ethical guidelines, the ethics committees that conducted the first review is responsible for carrying out the supplementary review. Currently, the following factors are used to determine which ethics committee is assigned to a specific research project: whether the study 1) is a registered clinical trial or ancillary research, 2) is compliant with the Act on Securing Safety of Regenerative Medicine or the Clinical Research Act, 3) is a multicenter or a single-center project, 4) includes NMS as a representative or participating institution in cases of multicenter projects, 5) involves international collaboration, 6) involves human genome or genetic analysis, 7) is an interventional or a non-interventional study (observational research), and 8) involves patients or staff members of NMS hospitals. The flowchart used to select the appropriate ethics review committee is shown in **Figure 2**.

If, as mentioned above, a batch review of a multicenter study involving an NMS hospital has been carried out by an external ethics committee, there is no need for it to be re-reviewed by the NMS Foundation. It should be noted, however, that not all external ethics committees can be considered reliable, so favorable batch reviews obtained only from those designated by the Central Ethics Committee as providing a high level of review quality obviate the need for re-review by NMS. A list of external ethics committees approved by the Central Ethics Committee is posted as an "Allowlist" on the NMS website[7].

Case reports are not subject to ethical review requirements, but some journals' editorial boards may request an ethical evaluation by an institutional ethics committee. In such cases, review applications should be submitted to the appropriate ethics committee. Additionally, if an investigator wishes to request an ethical review for any reason, a request can be submitted for consideration

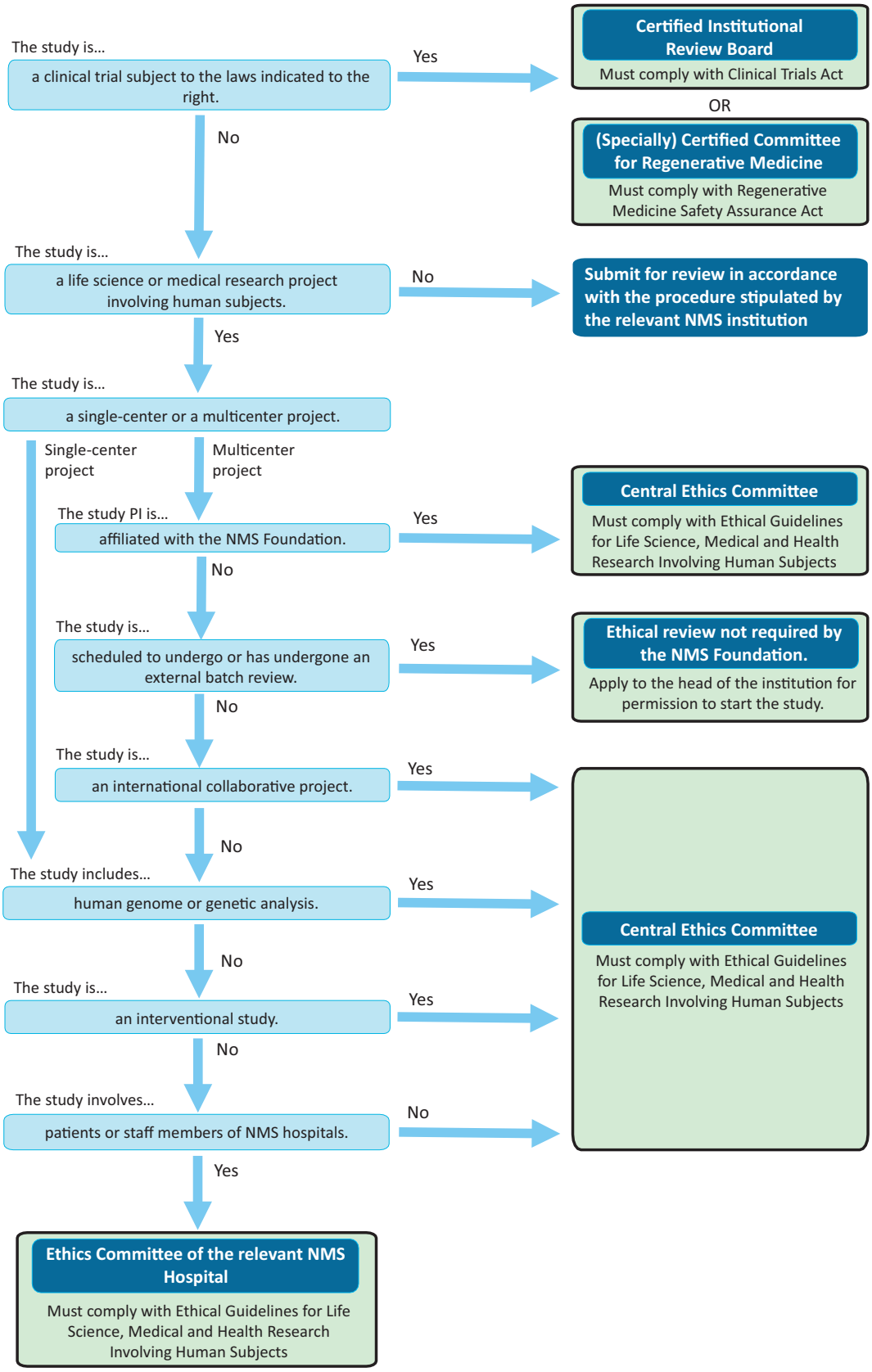

Fig. 2 Flowchart used to select appropriate ethics committees at NMS; registered clinical trials and ancillary research are excluded because they are reviewed by the institutional review board at each NMS hospital.
NMS: Nippon Medical School, PI: principal investigator

based on the reasons provided by the investigator.

This report outlines NMS's current ethical review processes for research involving human subjects, but it is important to note that the processes are subject to change in line with future revisions of relevant Japanese laws, guidelines, and local regulations. It is vital that NMS investigators keep themselves informed about the latest developments in the ethical review processes and ensure that any research projects they undertake are subjected to an appropriate ethical review before the research is initiated. They should remember that failure to do so is a serious violation of laws, guidelines, and local regulations, and that it might render them subject to criminal penalties, administrative sanctions, or disciplinary action from the NMS Foundation.

Conflict of Interest: None.

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