

The Japanese Society of Gastroenterology (JSGE) Policy on Conflict of Interest in Medical Research

Introduction

A remarkable progress in medicine and healthcare from the latter half of the 20th century resulted in the development of many new methods of treatment and prevention. In Japan, the enactment of the Healthcare and Medical Strategy Promotion Act and the Act on Japan Agency for Medical Research and Development as a national policy in 2014, and subsequent establishment of Japan Agency for Medical Research and Development in April 2015, expanded strategic approaches in the development of innovative drugs, biological drugs, and medical equipment and devices and in the promotion of regenerative medicine through academic-industry-government collaboration. The participation of the academia in regenerative medicine and entrepreneurship in relation to medical equipment and devices are beginning to bear fruits and giving vigor to clinical development.

The Japanese Society of Gastroenterology (hereafter called “JSGE”) is engaged in activities involving human subjects (including their samples and data) towards maintaining and promoting national health and improving the prognosis and the quality of life of patients. To this end, JSGE draws up various medical guidelines through identification of causes of diseases, understanding of pathological conditions, prevention of diseases, and verification and improvement of the effectiveness of diagnostic and therapeutic methods used in healthcare. Further promotion of academic-industry collaboration is extremely important from the standpoint of evidence-based medicine and medical economics and in fulfilling social responsibility of JSGE.

The more researchers at public entities, such as research institutes and academic societies, promote academic-industry collaboration through medical research, the deeper they will become involved in the activities of specific companies. As a result, a clash or conflict inevitably and unavoidably arises between the researcher’s social responsibility to work for the public good and the personal interest gained from academic-industry partnership activities. This resultant state is called “conflict of interest (COI).” In promoting academic-industry partnership, an important challenge for academic institutions and societies is to organizationally and appropriately manage such states of conflict of interest. If those engaged in medical research fall short of appropriately declaring a serious conflict of interest existing in relation to funding companies or organizations, it could increase the risk of bias, endanger the human rights and personal safety of the research subjects, and warp the research methods, data analysis, and interpretation of the results. In fact, a scandal over the antihypertensive drug valsartan in 2013 threw into doubt the credibility of the quality of clinical studies at five universities in Japan. The scandal came about as a result of obscure arrangements in corporate donations and acceptance of data management and statistical analysis services, and contracts and other safeguards were not used to appropriately manage bias risks. Data were willfully manipulated to fabricate a conclusion advantageous to the pharmaceutical company involved. A number of research papers published in international journals had to be withdrawn,

tarnishing not only the quality but also the credibility of the medical guidelines in question. Partly to prevent such scandals, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labor and Welfare of Japan published the Ethical Guidelines for Medical and Health Research Involving Human Subjects, on December 22, 2014, by integrating existing ethical guidelines on clinical research and epidemiological research. The new guidelines, in particular, clarified the responsibility of the head of research institute and principal investigator conducting research on interventions, and sought to strengthen ethics examination, monitoring, auditing, and COI management. Meanwhile, the Association of Japanese Medical Colleges (AJMC) also published the Guidelines for Investigator-Initiated Clinical Trials, in February 2015. The AJMC guidelines focused particularly on research on invasive interventions using approved drugs, and illustrated concrete steps from planning to appropriate conduct of clinical trials (including public registration of clinical trials, data management, statistical analysis, data interpretation, and preparation of theses). The AJMC guidelines also deal with COI management by using concrete examples, to assure quality and reliability of clinical trials that allow involvement of enterprises. Subsequently, the Clinical Trials Act came into effect as of April 2018. This law defined (1) clinical trials of unauthorized drugs, drugs for off-label use, etc. and (2) clinical trials of a pharmaceutical company's drug, etc. conducted with funding from the same pharmaceutical company as "specified clinical trials," and obligated for clinical trials carried out to validate the efficacy and safety of the drugs, etc. a set of processes for the conduct of the clinical trials, management of conflict of interest, measures for ensuring review and comments from a certified clinical trial review committee, and public disclosure of information about funding for the clinical trials.

Japan Pharmaceutical Manufacturers Association published the Transparency Guideline for the Relation between Corporate Activities and Medical Institutions in 2011, and its member companies began to disclose the amount of funding they provide to medical institutions, research institutes, other types of medical organizations, foundations, and healthcare-related individuals on their websites as from 2013. In the United States, a government agency discloses details about beneficiaries and amounts of funding from pharmaceutical companies in an "open payment program." Last year, a stir was caused when the media reported on an omission by a well-known American physician to disclose a significant state of conflict of interest in a paper published in a world-class international journal. In Japan, too, it is possible to do online searches to find details about financial relations between companies and physicians. Academic societies in the field of clinical science are expected to meet a rigorous standard of COI management of individuals participating in development of medical guidelines and to fulfill its accountability if any discrepancies are found in the contents of their COI disclosures.

On the other hand, research institutes are also involved in development of approaches for prevention, diagnosis or treatment of diseases and are strengthening their efforts to use the results of such research to grant licenses to companies or to establish university spin-offs, and in that sense, research institutes are required to contribute to society and public good. If a publicly funded research

institute has ownership of patents or stocks of a manufacturing company or a distribution company, a conflict of interest may potentially arise. As a result, if senior directors of that research institute who have authority over decision-making or auditing of the institute's activities decide to give priority to the interest of the institute, it may distort the integrity and reliability of the research, increasing risk to the research subjects and patients. If the research institute becomes involved in promoting the distribution of such drugs and medical equipment preferentially over other drugs or medical equipment, it may be perceived with suspicion that it is trying to make wrongful gains or increase its revenues through publication of a thesis.

To ensure objectivity, fairness, and integrity of research institutes, the American Association of Medical College (AAMC) and American Association of Universities (AAU) published guidelines in the United States regarding institutional conflict of interest of research institutes (hereafter called "institutional COI") in 2002, and proposed a model policy for management of institutional COI in clinical research involving human subjects in 2008. The National Science Foundation (NSF) (2005) and the National Institutes of Health (NIH) (2013) each requires individual researchers to disclose institutional COI. In 2013, the International Committee for Medical Journal Editors (ICMJE) published the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which are now used as a standard in some 6,000 medical journals around the world. ICMJE also requires disclosure of the author's personal conflict of interest as well as institutional COI of the author's affiliated research institute in its COI disclosure form required for submission at the time of publication of a thesis. In Japan, the Association of Japanese Medical Colleges (AJMC) published the Guidance for Management of Institutional Conflict of Interest in 2018, in which it emphasized the importance of disclosure and management of institutional COI in clinical research. Considering these trends, the Japanese Association of Medical Sciences has published a partially revised version of the Guidelines on COI Management in Medical Research.

To ensure quality and reliability of medical research, JSGE will appropriately manage conflict of interest and fulfill our accountability to society, by enforcing its members to thoroughly abide by JSGE's COI guidelines. JSGE's COI guidelines have been substantially revised to maintain consistency with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the Clinical Trials Act and in consideration of COI management trends in and outside Japan.

I. Objective

Considering that JSGE is required to fulfill its social responsibility and maintain a high level of ethical standards in all of its medical research involving academic-industry collaboration, JSGE drew up the Policy on Conflict of Interest in Medical Research (hereafter called the "Policy"). The Policy's objectives are to have JSGE members appropriately manage their states of conflict of interest when engaging in medical activities, so as to manage bias risks in the conduct of research, presentation of research results, development of medical guidelines, and dissemination and

education of the research results and medical guidelines, to promote sound academic-industry collaboration while maintaining impartiality and integrity, and to fulfill its social responsibility by contributing to advancing progress in prevention, diagnosis, and treatment of diseases in the field of gastroenterology. The Policy, therefore, presents basic principles on COI management to JSGE members and others concerned, and requires them to voluntarily and properly disclose their state of conflict of interest and abide by the Policy when participating in various JSGE projects. Needless to say, members should also observe employee rules and regulations and COI guidelines of the research institutes, etc. they are affiliated with.

Basic concepts in COI management of research institutes and researchers are as follows:

- (1) Based on the presumption of ensuring ethical, medical, and scientific integrity of medical research through academic-industry collaboration, research institutes and researchers accepting external funding (donations or agreement-based research funds), drugs, medical equipment and devices, and/or services from companies, organizations, and individuals who have interest in the research, will do so in an appropriate manner by concluding an agreement where necessary (to clarify consideration and/or responsibility over research outcomes). However, while the Clinical Trials Act is applicable to a researcher-led clinical study that uses external funding obtained from a company or organization that refuses to take responsibility over the research outcomes, research institutes and researchers must avoid entering into an agreement that will enable such a funding organization to exercise influence on the interpretation of the results of the clinical study or on the publication process, as such an agreement will compromise the independence and integrity of the study.
- (2) To ensure quality and reliability of the research results, research institutes and researchers will appropriately disclose the contents of the agreement (e.g. sources of funding, role of the funding organization, and the state of conflict of interest of the research institutes and the researchers), and take precautionary measures so that their state of conflict of interest does not develop into a problem. Research institutes and researchers will accurately state and make public such information in research protocols, IC forms, and theses.
- (3) If a question is raised by society at large about the contents of a thesis, the corresponding author must fulfill their accountability jointly with related companies.
- (4) For a research institute to ensure the quality as well as reliability and integrity of its medical research, education, and medical practice, it must keep transparent its relations with interested parties by disclosing the institutional COI of the research institute as well as of the ties between its senior directors and specific companies and for-profit organizations.

II. Persons covered by the Policy

The Policy applies to the following persons to whom a state of conflict of interest may arise:

- (1) JSGE members
- (2) Persons making presentations at the JSGE's academic lectures, etc. (including those who are

not JSGE members)

- (3) JSGE's officers (Director General, Directors and Auditors), Executive Councilors, Council Members, organizers of academic lectures, etc. (presidents, etc.), chairpersons of various committees, members of specific committees (such as the Consideration Committee for Scientific and Educational Meetings, Journal Editorial Board, committees involved in development of medical guidelines, Ethics Committee, Medical Malpractice Indemnity Committee, and Committee on Conflict of Interest), and members of nonpermanent working groups (such as subcommittees and working groups)
- (4) JSGE's administrative staffs
- (5) Spouses, first-degree relatives, and all persons sharing the incomes and properties of any person mentioned above from (1) to (4)

III. Activities covered by the Policy

The Policy applies to all activities of JSGE, including, without limitation:

- (1) Organization of academic lectures (including annual general assemblies), academic lectures organized by JSGE branches, etc.
- (2) Publication of JSGE journals, scientific books, etc.
- (3) Development of medical guidelines, etc.
- (4) Research, surveys, and investigations
- (5) Encouragement of research and commendation of research achievements
- (6) Administration of the certification system for gastroenterologists (certification of gastroenterologists and accreditation of hospitals, etc.)
- (7) Promotion of lifelong learning activities
- (8) Communication and cooperation with related academic societies
- (9) Communication and cooperation with for-profit organizations, companies, etc.
- (10) Promotion of international research cooperation
- (11) Advances in gastroenterology, implementation of such advances in society, and promotion of activities to inform the public about health care
- (12) Any other activities required for the achievement of the JSGE's objectives (e.g. work of ad-hoc investigation committee and advisory committee)

In particular, disclosure of the state of conflict of interest with related companies in the last three years must be made using a prescribed form when giving presentation or making publication for the following activities:

1. Making presentations at academic lectures organized by the JSGE (such lectures hereafter called the "lectures, etc.")
2. Publishing articles in JSGE journals and other publications
3. Preparation of medical guidelines and manuals
4. Academic activities that are unrelated to JSGE's projects and making presentations at lectures,

round-table discussions, luncheon seminars, evening seminars, and the like

As for lectures, etc. hosted or co-hosted by a company, the chair or moderator must also disclose his or her state of conflict of interest.

“Medical research,” as it relates to presentations, is defined as basic or clinical research, subject to ethical screening, that is conducted for the purpose of improving methods of prevention, diagnosis, or treatment of diseases in healthcare, understanding the causes of diseases and their pathology, and improving the quality of life of patients. Medical research involving human subjects, which includes research conducted on human-derived samples and data that could be used to identify specific individuals, will be governed by the Ethical Guidelines for Medical and Health Research Involving Human Subjects, published on December 22, 2014 by the MEXT and the Ministry of Health, Labour and Welfare.

IV. “Companies, corporate organizations, and for-profit organizations related to medical research” means companies and organizations having the following relations with the medical research:

- (1) Companies and organizations requesting the conduct of the medical research or jointly conducting the medical research (regardless of whether or not payment will be made for the research)
- (2) Companies and organizations owning patents and other rights related to a treatment method, drug, equipment or device that is being subjected to assessment in the medical research
- (3) Companies and organizations providing a drug, equipment or device that is used in the medical research, either for free or at a substantially discounted price
- (4) Companies and organizations providing a research grant or donation for the medical research
- (5) Companies and organizations providing a drug, equipment or device that is pending official approval for use in the medical research
- (6) Companies and organizations providing funds for endowed chairs, etc.

V. Matters for COI disclosure and disclosure standards

Covered in this section are individuals required to make COI disclosure as well as such individuals’ affiliated research institutes or the heads of the affiliated research institutes or divisions with whom the individuals, now or in the past, were in a relation of a co-investigator or research collaborator.

For the personal COI disclosure, if the person corresponds to any one of (1) to (9) below in excess of the threshold set for disclosure, that person must make the disclosure using a prescribed form (JSGE Form 3-A, B). The amount set for each item of COI disclosure is based on the following standards:

- (1) As for appointment as a board member or advisor of a company, corporate organization, or for-profit organization (hereafter collectively called “a company or organization”) that is related to medical research, an annual compensation of ¥1 million or more from any one company or organization
- (2) As for ownership of corporate stocks, an annual profit (an aggregate of dividends and capital

gain) from one company's stock of ¥1 million or more, or ownership of 5% or more of all shares of the company's stock

- (3) As for patent royalties received from a company or organization, an annual royalty payment of ¥1 million or more for use of one patent
- (4) As for per diem (honorariums, etc.) paid by a company or organization for the time and energy spent by a researcher to attend or give a presentation or advice at a meeting, a total amount of ¥500,000 or more of honorariums received from one company or organization in a year
- (5) As for fees paid by a company or organization for writing a pamphlet, article based on round-table discussions, etc., a total amount of ¥500,000 or more in fees received from one company or organization in a year
- (6) As for research grants from a company or organization, the research grants are awarded by one company or organization for medical research (joint research, commissioned research, clinical trial, etc.) and the total contracted amount for research that the individual making the COI disclosure essentially has discretion over their use is ¥1 million or more in a year
- (7) As for scholarship grants from a company or organization, the scholarship grants are awarded by one company or organization to the individual making the COI disclosure or to the chair, field, or laboratory the individual is affiliated with and the total amount of the grants that the individual making the COI disclosure essentially has discretion over their use is ¥1 million or more in a year
- (8) As for endowed chair from a company or organization, the individuals making the COI disclosure are affiliated with the endowed chair, and the total amount of the endowment that the individuals making the COI disclosure essentially have discretion over its use is ¥1 million or more in a year
- (9) As for free trips and other gifts unrelated to research, education, and healthcare that are provided by a company or organization, a total amount of ¥50,000 or more provided from one company or organization in a year

The "appointment as a board member or advisor of a company or for-profit organization" in (1) above applies when a researcher affiliated with a research institute assumes the office of a board member or advisor of a specific company under contract to regularly and continuously work for that company and receive remuneration. If advice, etc. is given at the request of a company in discontinuous, isolated instances, the COI disclosure should be made in accordance with (4) "per diem, honorariums, etc. paid by a company or for-profit organization for the time and energy spent by a researcher to attend or give a presentation or advice at a meeting" above.

In addition, as for (6) and (7) above, disclosure is also necessary if research grants or scholarship grants from related company or organization are awarded to the department (chair, field, etc.) or laboratory the individual is affiliated with. It is also clearly indicated that the threshold for such disclosure of research grants or scholarship grants from related company or organization is based on the amount that the individual making the COI disclosure essentially has discretion over

their use. The specific methods for disclosure and publication will be as stipulated in the prescribed forms.

As for institutional COI disclosure, if the person required to make COI disclosure is or was in a relation of a co-investigator or research collaborator either with the research institute the person is affiliated with or with the head of the affiliated research institute or division (e.g. university, hospital, faculty, center, etc.), now or in the past, and if such a relation may have an influence on JSGE activities that the person is involved with, then that person is required to make the institutional COI disclosure using the prescribed form (JSGE Form 3-C) for the items shown below. The amount set for each item of institutional COI disclosure is based on the following standards:

- (1) As for research grants from a company or organization, the research grants are awarded by one company or organization to the research institute or division or the head of the research institute or division the individual is affiliated with and the total amount of the grants that the research institute or division or its head essentially has discretion over their use is ¥10 million or more in a year
- (2) As for donations from a company or organization, the donations are awarded by one company or organization to the research institute or division or the head of the research institute or division the individual is affiliated with and the total amount of the donations that the research institute or division or its head essentially has discretion over their use is ¥2 million or more in a year
- (3) In addition, if the research institute or division or the head of the research institute or division the individual is affiliated with owns a company's stocks (5% or more of the issued shares of the company), has received patent royalties from a company or organization, or has any investment outstanding in a company or organization, these must be disclosed.

VI. Notice on medical research and, in particular, invasive intervention research

- (1) Clinical trials for approval of new drugs must be carried out in compliance with the Good Clinical Practice (GCP). A researcher-led large-scale intervention study using a drug that has already been put on the market is conducted for the purpose of verifying efficacy and safety of the drug, promoting appropriate use of the drug in the clinical setting, and providing important information and evidence for standard treatment, and such research must be conducted based on ethical guidelines. As for the latter studies on already marketed drugs, it has been pointed out that companies, in view of promoting sale of their products, have a high level of interest in supporting post-marketing clinical studies by way of funding or providing labor and services, and that this tends to increase bias risk in such studies and the potential for scandals. JSGE members must abide by the "Declaration of Helsinki," the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the Clinical Trials Act, COI guidelines, the AJMC Guidelines for Investigator-Initiated Clinical Trials, and related laws and regulations. JSGE members are required to pay special attention to protecting the human rights and lives of research subjects when conducting any intervention study.

- (2) When JSGE members voluntarily conduct a researcher-led invasive intervention study, oftentimes they will have opportunities to use external funding, drugs, medical equipment and devices, and services of experts with technical knowledge and skills, provided by companies, organizations, and individuals. Where such clinical research is based on an agreement and has the institute of the member's affiliation acting as the contact point, such research should be carried out as joint research or commissioned research, the responsibility of the fund provider on the research outcomes should be made clear, and any restrictions on the use of such funds, drugs, medical equipment and devices, and services, considerations, and division of roles should be clearly written down. On the other hand, where there are no restrictions on the use of scholarship grants or research funds, JSGE members can accept such scholarship grants or research funds for use in a researcher-led clinical study. If external funding for joint research, commissioned research, or unrestricted scholarship grant is to be used for intervention research and if such funding is equal to or above JSGE's prescribed COI threshold, JSGE members must clearly indicate the provider of such a funding source and such provider's role in the clinical research, on the principle of making such information public and ensuring transparency.
- (3) Making results of medical research widely available for use by healthcare professionals, patients, and others benefits the public. Therefore, when conducting medical research involving human subjects, JSGE members must register the research on a public database and publish the results of the research, in principle, in the form of a thesis.
- (4) When preparing and publishing a thesis, JSGE members must clarify authorship, bearing in mind international standards on authorship, namely, the ICMJE Recommendations. Non-author contributors, such as medical writers, statisticians, and other contributors, their affiliation, and sources of funding should be mentioned in the "Acknowledgement." In addition, if any interested party is providing labor or services based on an agreement to assist in the conduct of clinical research or in the preparation of a thesis and their involvement is anticipated to influence the contents of the thesis, the roles played by each of such interested parties must be clearly stated in the section "Role of the funding source" (Fig. 1) to ensure transparency. Other forms of interest must also be stated and disclosed. In particular, if suspicion of any wrongdoing is raised by a third party, both the principal investigator and the companies concerned must jointly fulfill their accountability.
- (5) When a researcher affiliated with a company is dispatched to work in a research institute as a researcher, graduate student, part-time lecturer, and the like, and such a researcher is to give a presentation on the research results or publish the research results in a thesis, such a researcher must also clearly state the name of the company he or she is affiliated with.
- (6) If a person who had been working for a company leaves his or her job to work for a research institute and such a person is to present or publish results of research that pertains to the company he or she had been working for, such a person must clearly state the name of such a company alongside the name of the research institute he or she is currently affiliated with, for a

period of five years after leaving the company.

VII. Matters to be avoided in relation to the state of conflict of interest

1. Matters to be avoided by all persons covered by the Policy

Activities such as publication of medical research results (such as presentation at academic meetings and publication of theses) and preparation of medical guidelines, which contribute significantly to raising the quality of healthcare in our country, should be based purely on scientific evidence and judgment and carried out in the interest of the public. In publishing medical research results and interpretations and preparing medical guidelines and manuals (on diagnosis, treatment, prevention) based on scientific evidence gained from medical research, JSGE members and other persons covered by the Policy must not be influenced by any arbitrary objectives of the person or company funding the medical research (such as unjust inducement of transactions or sale), nor must they enter into an agreement with the provider of funding that will make such influence unavoidable.

Specifically, the following should be avoided:

- (1) Receiving out-of-contract incentive payment for acting as an intermediary for or introducing human subjects in clinical studies
- (2) Receiving out-of-contract incentive payment for collecting cases within a specified period of time
- (3) Receiving out-of-contract performance-based payment for achieving specified research results

2. Matters to be avoided by principal investigators and research representatives

The principal investigator and research representative with rights to make decisions on the planning and implementation of medical research, and in particular, clinical trials (including those conducted to obtain government approval for drugs and medical equipment) should be selected from among researchers socially recognized as not being in a state of material conflict of interest in relation to each of the items shown below (in other words, having relatively little overlapping interest with the provider of funding). This condition concerning directorship should be maintained even after the selection of the principal investigator and research representative.

Specifically, the principal investigator and research representative, who have a duty to appropriately disclose monetary relations with the provider of funding, should take particular note of and avoid matters indicated below.

- (1) Owns the shares of the person or company providing funding for the research or is a director, etc. of such a company
- (2) Has the patent right over or is receiving patent fees for the drug, therapy, inspection method, etc. that is the subject of the research
- (3) Has received expenses for travel, accommodation, etc., other than for the legitimate reasons of participating in academic meetings, from the person or company providing funding for the research

- (4) Has received money and/or gifts outside legitimate remuneration for the time and efforts expended on the research
- (5) Even though a researcher affiliated to a company is dispatched to work in a research institute and participate in the research as a researcher, part-time lecturer, or graduate student, engage in such an inappropriate act as concealing the name of the company in the research plan or when presenting or publishing the research results
- (6) Is in a situation where the person or company providing funding for the research can exercise its influence over the collection, storage, statistical analysis, interpretation, or judgment of the research data
- (7) Enter into an agreement that allows the provider of funds or interested company to exercise influence on decisions to present research results at a scientific meeting or publishing research results in a thesis

However, if the talent of a researcher corresponding to any one of (1) to (4) above plays an important role in the planning and implementation of the medical research and, at the same time, the medical research has an extremely significant meaning socially, the researcher may be appointed as the principal investigator or research representative of the medical research, provided that equity and transparency of the principal investigator's or research representative's judgment and of the measures adopted by the principal investigator or research representative can clearly be ensured. In any event, accountability to society must be fulfilled.

If there is a possibility that a contract with a company contains matters described in (5) or (6) above, details on the role and involvement of the person or company providing funding for the research must be disclosed at the end of the thesis when publishing the research results.

VIII. Method of conduct

1. Responsibilities of JSGE members

All JSGE members making presentations of medical research results at academic lectures, etc. must properly disclose, at the time of the presentation, the state of conflict of interest related to the implementation of the research, using JSGE's prescribed form. If, in relation to the presentation of the research, etc., any allegation is made concerning violation of the Policy, the member in question must take note of the allegation and provide full cooperation. The JSGE Board of Directors (the Director General) will refer the matter to the committee with jurisdiction over conflict of interest (hereafter called the "Committee on Conflict of Interest") for deliberation and will, based on the report of the Committee on Conflict of Interest, take reasonable steps.

2. Responsibilities of officers, etc.

JSGE's officers (the Director General, Directors and Auditors), Executive Councilors, Council Members, organizers of academic lectures (presidents, etc.), chairpersons of various committees, members of specific committees, and members of working groups are vested with important roles and

responsibilities concerning all activities of the JSGE. As such, they must voluntarily submit a written statement on their state of conflict of interest (covering the period of three years up to the year prior to the year of appointment) that they may have in relation to the activities of JSGE at the time of their appointment to their respective posts using a prescribed form (Form 3). If any change arises to the state of conflict of interest during the year of appointment or thereafter, they must provide additional disclosure addressed to the Director General, using Form 3, within eight weeks of such a change. The Director General must engage in the appropriate personnel management of JSGE officers, etc. in order to maintain fairness and impartiality of the activities of JSGE.

All officers (including chief editors and members of the Editorial Board) are required to voluntarily submit a written statement about their state of conflict of interest at the time they assume office. Peer reviewers, including members of the Editorial Board serving as peer reviewers, will also be subject to COI management. Basically, when asking any individual to serve as a peer reviewer, judgment on whether or not there is a state of conflict of interest between the peer reviewer candidate and the author of a contributed paper should rest with the peer reviewer candidate, and any peer reviewer candidate will be allowed to decline the offer of serving as a peer reviewer if the candidate considers that he or she cannot fulfill COI accountability vis-à-vis the peer review outcomes. Dissemination of research results through academic lectures and journals is an important avenue through which such results can be put to the good of society. Accountability on the integrity and impartiality of such results must ultimately be borne by the Director General.

3. Role of the Committee on Conflict of Interest

For the purpose of avoiding bias risk in relation to appropriate promotion of medical research, publication of theses on research results, and development of medical guidelines through academic-industry collaboration, the Committee on Conflict of Interest fulfills an advisory role in the proper management of state of conflict of interest from the standpoint of researchers. If a state of material conflict of interest arises to a JSGE member in relation to any activities of the JSGE or if it is pointed out that there are inaccurate or uncertain points in the contents of a JSGE member's voluntary disclosure of conflict of interest, the Committee on Conflict of Interest will make an inquiry by holding a hearing, etc. to appropriately manage the state of conflict of interest of the JSGE member concerned, and report its findings to the head of JSGE.

The Committee on Conflict of Interest, at the request of the Director General, oversees the tasks shown below and reports to the Director General.

- (1) Responding to questions and requests from individual members who are in a state of conflict of interest (preparation of Q&As)
- (2) Assessing bias-risk-related state of conflict of interest in the activities of officers, presenters (including non-JSGE members), and participants in the development of medical guidelines, and providing advice and supervision
- (3) Cooperating in the planning of educational courses on research and publication ethics and

promoting educational activities

- (4) Tasks related to conducting investigation and recommending steps for remedy when there is suspicion of wrongdoing regarding COI disclosure made by individual members
- (5) Tasks related to review and revision of COI guidelines each time the Japanese Association of Medical Sciences's Guidelines on COI Management in Medical Research and the Japanese Society of Internal Medicine's Policy of Conflict of Interest in Medical Research are updated.

4. Role of the Director General

If a state of material conflict of interest arises in the execution of any activities of JSGE by officers, etc. or if it is recognized that any voluntary disclosure of conflict of interest to be inappropriate, the Director General must refer the matter to the Committee on Conflict of Interest and, based on the report of the Committee on Conflict of Interest, instruct steps to be taken to remedy the situation. The Director General must educate JSGE members so that if they are contributing an article to a non-JSGE medical journal (particularly international medical journal), they should make appropriate disclosures using the journal's COI disclosure forms. If any suspicion of wrongdoing by a JSGE member is raised by a third party in a published medical journal, the Director General must promptly initiate response and make efforts to regain trust.

The Director General must, as an organization, appropriately and promptly deal with any suspicion of wrongdoing related to JSGE members' state of conflict of interest, and if, as a result of an inquiry, it is deemed that the suspicion or allegation is unfounded, the Director General must fulfill JSGE's accountability to society and as for the allegation made against the particular JSGE member in question, make efforts to regain and secure trust in that member by issuing JSGE's views and statements to society (e.g. by publishing such views and statements on its website). On the other hand, if such suspicion or allegation is validated, the Director General, needless to say, should disclose the results of the fact-finding inquiry and communicate JSGE's measures against recurrence.

5. Role of the organizer of academic lecture

When presenters (including non-JSGE members) give presentations on the results of medical research at academic lectures, the organizer of the academic lecture (the president) must check that the presenters have appropriately completed their COI disclosure using a prescribed form. In particular, when a presentation is to be made on the results of research in which there is involvement of a company, it is the role of the organizer to provide an environment for the audience to judge whether or not the presentation of the contents of the research is being done in an impartial and equitable manner. The organizer may take steps to debar delivery of any presentation that runs counter to the Policy or that does not have COI disclosure. In such a case, the organizer will promptly notify the presenter concerned to that effect and provide reasons for the decision. The organizer may refer such cases to the Committee on Conflict of Interest, and based on the report of the Committee

on Conflict of Interest, may instruct steps to be taken to remedy the situation.

As for luncheon seminars, evening seminars, workshops, and lectures hosted or co-hosted by a company or for-profit organization, the chair or moderator should also make effort to disclose to the audience the names of the companies and organizations he or she has relations with, using slides in a similar manner as the presenters and reading out the names of the companies. If there are too many companies to read out, appropriate steps must be taken such as by using a separate projector to disclose the name of the companies on a slide.

6. Role of the Journal Chief Editor

Basically, the Journal Chief Editor will fulfill its role in conformity with the Medical Journal Editorial Guidelines of The Japanese Association of Medical Sciences (2015). The basic principle is to ensure, from the point of view of COI management, that originally authored articles on medical research, reviews, medical guidelines, edited articles, opinions, etc. are published from an impartial standpoint, while maintaining scientific and ethical integrity, in JSGE journals and other publications. The Journal Chief Editor must check whether such publication is in conformity to related ethical guidelines and the Policy, and ensure the quality as well as reliability of the contents of the articles.

False statement in a published paper may come to light, and misgivings may arise concerning honesty and integrity of research. In response to questions of research honesty and integrity or an allegation of misconduct, the Japanese Association of Medical Journal Editors (JAMJE) recommends editors to follow the procedures published by the Committee on Publication Ethics (COPE) (<http://publicationethics.org/>), which include COI disclosure.

1) COI management of contributed papers

In the publication of a thesis, the basic principle is to promote additional transparency in the relation of interest between the author and any company by requiring disclosure of concrete information on the roles of the author, the company, and any persons associated with the company in the process of conducting the research and publishing the results of the research (including research funding, research planning and design, preparation of a research protocol, data tabulation and processing, data management and analysis, and preparation of the thesis) as well as the author's state of conflict of interest. In addition, it is necessary to ensure impartiality and equity, from a third-party perspective, in the contents of the research. All authors must bear responsibility for the quality and reliability of the published research results. It is society at large (including its citizens, patients, and physicians) who will be the judge of the published research results. For this reason, it is essential to ensure transparency of research.

(1) Authors in Japanese-language journal

As contributors to JSGE's Japanese-language journal are mostly JSGE members, it suffices that the same COI disclosure items as those used for JSGE's academic meetings and lectures be used.

As for contributors who are not JSGE members, their consent to abide by JSGE's COI guidelines must be obtained, and all contributors must disclose their state of conflict of interest using a prescribed form.

(2) Authors in English-language journals

The COI disclosure forms required from authors for publication of theses in academic journals will be in compliance with the Japanese Association of Medical Sciences's Medical Journal Editorial Guidelines and the Japanese Association of Medical Sciences's Guidelines Concerning Conflict of Interest (2017). Both guidelines are consistent with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals published by the International Committee of Medical Journal Editors (ICMJE) (updated after 2013 as needed). At JSGE, the English Journal Editorial Board prepares its COI disclosure forms by referencing the COI disclosure forms proposed by ICMJE. To ensure fairness and reliability of research, the author must disclose, using prescribed forms, his or her state of conflict of interest with companies, etc. having involvement in the contents of the thesis. For medical research conducted with a company under a contract, the role and involvement of the person providing funding (any persons associated with the company, etc.) in the planning, protocol design, execution, monitoring, auditing, data tabulation, statistical analysis, data interpretation, writing of the thesis, and review must be clearly indicated in the "Role of the funding source" section or in the "Acknowledgement" of the thesis. From the point of view of authorship, it is also required to clearly indicate in the "Contributors" section of the thesis the roles and contributions of individual authors in the process from research planning to thesis publication.

Examples are shown below for theses in English and Japanese (Figure 1). On the other hand, even if there is no state of conflict of interest that needs to be disclosed, a statement such as "The authors state they have no conflicts of interest" must be indicated at the end of the thesis.

2) Response to COI transgressor

If, after publication of a thesis, the Editorial Board is informed of any violation of the Policy related to the thesis (such as disclosure of false information), the Editorial Board will work with the Committee on Conflict of Interest to ascertain the facts. In cases where there is actual violation of the Policy, the process recommended by the Committee of Publication Ethics (COPE) will serve as reference. The Editorial Board will ascertain the facts with the author and may, with the understanding of the Director General, take such steps as to request corrective action, retract the thesis from publication, request withdrawal of the thesis, and request issuance of a statement of apology for publication, in accordance with the gravity of the breach. In such a case, the Editorial Board must promptly notify the author concerned to that effect and provide reasons for the decision. The Editorial Board may also make that fact public in the publication concerned in the name of the Editorial Chief Editor.

Figure 1. COI Disclosure Statement When Publishing Results of Research Supported by a Pharmaceutical Company under a Contract

1) Example for a thesis in English

● Role of the funding source:

ABC company participated in the interpretation of data and review of the report.

● COI disclosure: author's disclosure

● Acknowledgment:

Financial support for the clinical trial was provided by ABC company (Tokyo, Japan).

This manuscript was reviewed by the funding company. We thank all the study investigators and staff and patients who participated in this trial, Ichiro Tokyo and Jiro Kyoto, of ABC company, for helpful discussions during manuscript development.

*Extracted from the Guidelines Concerning Conflict of Interest of the Japanese Association of Medical Sciences 2017

7. COI management in the preparation of medical guidelines, treatment guidelines, etc.

Medical guidelines on the correct use of drugs and medical equipment and devices and on standard treatment draw considerable interest in the medical community and are highly influential. Academic societies have published numerous medical guidelines, which have significantly contributed to improving the quality of care in our country. Physicians with expert knowledge and experience participate in committees that draw up such guidelines, but in many instances, such physicians have significant overlapping monetary interest with related companies. It has been pointed out that in such instances, publication and reporting biases are more likely to occur to the advantage of such related companies. COI management is necessary to dispel such concerns. It is, moreover, the perception of society at large that if an academic society has significant monetary interest with specific companies, bias risk will increase as a result. Therefore, JSGE will also disclose its own state of conflict of interest (institutional COI).

For the selection of the chair and members (including members from outside JSGE) of committees preparing medical guidelines, while experts should not be excluded from participating in the preparation of the medical guidelines, it is important that there is appropriate COI management through requiring all committee members participating in the development of medical guidelines (i.e. members of medical guidelines supervisory committee, medical guidelines development committee, and systematic review committee, and external reviewers) to disclose their states of conflict of interest (COI disclosure forms related to JSGE-CPG development). The states of conflict of interest of all members of the committees involved in the preparation of the guidelines as well as of the academic society that is preparing the guidelines must be disclosed in the guidelines, using Tables 1 and 2, respectively, of the Japanese Association of Medical Sciences's COI Management Guidance on Eligibility Criteria

for Clinical Practice Guideline Formulation (2017).

For those committee members whose state of conflict of interest does not exceed any one of the thresholds indicated in Table 3, they can be appointed as chairpersons of the committees and have voting rights, but if their state of conflict of interest exceeds any one of the thresholds indicated in Table 3, they cannot be appointed as chairpersons of the committees. In addition, if a state of conflict of interest of the person chosen as chairperson of a committee arises in excess of any of the thresholds, that person should consider withdrawing himself or herself from appointment as chairperson of the committee. On the other hand, individuals who do not exceed any one of the thresholds indicated in Table 4 may be appointed members of the committees and participate in the deliberations of the committees with voting rights. Even if an individual exceeds any one of the thresholds, provided that the committee chairperson decides that the individual is indispensable in developing the guidelines and the integrity and transparency of such a decision and measures taken thereof can be clearly guaranteed, the individual may be allowed to report the actual amount in excess to the Committee on Conflict of Interest, which will then ascertain the amount and have consultations with the guidelines supervisory committee. If approved through the consultation, the individual is allowed to participate in the committee deliberations as a committee member but should not be allowed to have any voting rights. If any state of conflict of interest of any candidate committee member is substantially above any one of the thresholds of Table 4, such a candidate should consider withdrawing himself or herself from being appointed as a committee member.

Table 1. Examples of COI Disclosure Statements of Participants in the Preparation of Medical Guidelines

| COI disclosure of members of a medical guidelines executive committee | | | | | | | | | |
|---|-------------|---|----------------------|----------------------|----------------------|---------------------|------------------------|-------------------|------------|
| Participant | (1) Advisor | (2) Ownership of/profit from corporate stocks | (3) Patent royalties | (4) Honorariums | (5) Article fees | (6) Research grants | (7) Scholarship grants | (8) Endowed chair | (9) Others |
| Hanako Tokyo, Professor, Y Chair, XX University | | Pharma A | | Pharma B Pharma D | Pharma A | Pharma C | Pharma B Pharma E | | |
| Taro Tokyo, Associate Professor, U Chair, TT University | | Pharma F | | Pharma B Pharma D | Pharma A Pharma H | Pharma C | | Pharma G | |

| COI disclosure of members of a medical guidelines preparation committee and a systematic review team | | | | | | | | | |
|--|-------------|---|----------------------|----------------------------------|----------------------------------|---------------------|------------------------|-------------------|------------|
| Participant | (1) Advisor | (2) Ownership of/profit from corporate stocks | (3) Patent royalties | (4) Honorariums | (5) Article fees | (6) Research grants | (7) Scholarship grants | (8) Endowed chair | (9) Others |
| Umeko Osaka, Director, N Dept., MM Hospital | | | | Pharma C Pharma D Pharma C | Pharma H Pharma E | Pharma B | | | |
| Jiro Osaka, Professor, P Chair, OO University | | | | Pharma A Pharma A Pharma F | Pharma B Pharma C Pharma B | Pharma B | Pharma G Pharma H | | |

The Japanese Association of Medical Sciences COI Management Guidance on Eligibility Criteria for Clinical Practice Guideline Formulation 2017

Table 2. COI Disclosure of the Breakout Group Preparing the Medical Guidelines (example)

| |
|---|
| 1) Names of companies that provided funding (donations, etc.) in relation to the activities of the breakout group |
| Pharma A, Pharma B, Pharma C, Pharma D, Pharma E, Pharma F |
| 2) Names of companies that provided funding in relation to the preparation of the medical guidelines |
| Pharma C, Pharma E, Pharma F |

Table 3. Thresholds on Assumption of Office of Chairperson of the Supervisory Committee and Medical Guidelines Development Committee

| Personal Conflict of Interest of the Chairperson of the Medical Guidelines Development Committee | | | |
|--|-----------------------------|--------------------|-----------------------|
| 4. Honorarium | 5. Writing a pamphlet, etc. | 6. Research grants | 7. Scholarship grants |
| ¥1 million | ¥1 million | ¥10 million | ¥5 million |

Table 4. Thresholds on Voting Rights of Members (excluding the committee chairperson) of the Supervisory Committee and Medical Guidelines Development Committee

| Personal Conflict of Interest of Those Participating in Preparation of Medical Guidelines | | | |
|---|-----------------------------|--------------------|-----------------------|
| 4. Honorarium | 5. Writing a pamphlet, etc. | 6. Research grants | 7. Scholarship grants |
| ¥2 million | ¥2 million | ¥20 million | ¥10 million |

8. Institutional COI management of JSGE

Cases of institutional conflict of interest have been reported where senior directors (e.g. director general, director, etc.) in a relation of mentor-mentee, colleague, friend, or relative with the researcher in question, have been more liable to directly or indirectly influence medical research, particularly with regard to the conduct of clinical research involving human subjects, publication of those results, and development of medical guidelines. For example, if an academic society or its senior directors have received substantial donations from specific companies or own stocks of, or receive royalties from, specific companies, it can be anticipated under such circumstances in regards to the research results as well as the publication of the results and the development of medical guidelines that it would be more challenging to guarantee integrity, objectivity, and independence from the point of view of COI assessment and ethics. The Director General must centrally manage amounts paid by companies, corporate organizations, and for-profit organizations to JSGE per se (including at regional conferences) by recording in each accounting year the number of instances of payments made and their total amounts in each category of (1) research grants, joint research, and commissioned projects, (2) donations, and (3) income from academic conferences and meetings (e.g. company-related seminars and symposiums), and appropriately disclose such amounts as

institutional COI.

9. Others

The chairs and members of other JSGE committees will check that the JSGE activities they are respectively involved in are being carried out in accordance with the Policy, and if any violation of the Policy occurs in relation to the activities, they will promptly consider measures to remedy the situation. They may also refer such cases to the Committee on Conflict of Interest, and based on the report of the Committee on Conflict of Interest, the Board of Directors may determine steps to be taken to remedy the situation.

IX. Response to request for COI disclosure

If a request is made for disclosure of the state of conflict of interest of any JSGE member or officer from outside JSGE (e.g. the mass media, citizens' groups, etc.) and such a request can be considered reasonable, the Director General will refer the matter to the Committee on Conflict of Interest, which will look into the matter by conducting a fact-finding investigation while protecting the personal information of those concerned in the shortest time possible, and report back to the Director General. After receiving the report, the Director General will promptly respond to those parties that have made the request for disclosure.

If, after publication of a thesis on the results of medical research, an allegation is made concerning academic-industry collaboration pertaining to the thesis, the Editorial Board and Committee on Conflict of Interest will work in concert to shed light on the question at issue, and the head of JSGE will fulfill its accountability. If, however, the question at issue is beyond the capacity of either committee to handle, the head of JSGE will instruct an investigative committee, which will include members (learned persons) from outside JSGE, to expeditiously work towards clarifying the facts. Upon receipt of a report from the investigative committee, the head of JSGE should promptly fulfill its accountability to those requesting disclosure. If, on the other hand, a suspicion of misconduct is confined within the research institute in which the medical research in question was conducted, the head of JSGE should request the head of the research institute, to which the principal investigator (research representative) belongs, to investigate and report on the facts.

X. Measures against transgressors and filing of objection

1. Measures against transgressors

The JSGE Board of Directors reserves the right to deliberate on acts of violation of the Policy. If the Board of Directors decides, after first referring a case to the Ethics Committee and/or any other committee concerned and receiving their reports on the case and having deliberated on the case, that the case corresponds to a material breach of the Policy, the Board of Directors may take all or some of the following steps for a specified period of time in accordance with the degree of the breach.

- (1) Prohibit the transgressor from giving a presentation at any lectures organized by JSGE

- (2) Prohibit publication of the transgressor's thesis on any JSGE publication or retract the transgressor's thesis
- (3) Prohibit the transgressor from being appointed chair of JSGE's academic lectures
- (4) Prohibit the transgressor from participating in the Board of Directors or any of JSGE's committees or working groups
- (5) Dismiss the transgressor as JSGE councilor or prohibit the transgressor from becoming a JSGE councilor
- (6) Suspend the transgressor's JSGE membership, expel the transgressor from JSGE, or prohibit the transgressor from becoming a JSGE member

After the steps against the transgressor have been determined, that information will be shared with the heads of other related academic societies to which the transgressor belongs.

2. Filing of an objection

If the individual subject to penalties is unhappy with the decision, such an individual may request a review by filing with the JSGE secretariat an objection addressed to the Director General, within seven days of receiving a notification of the decision of the Board of Directors. In case where such a filing is made, the Director General of JSGE will promptly establish a committee for the review of the objection (a provisional advisory committee) and refer the case to the committee for deliberation. The Board of Directors will then deliberate on the committee's report and notify the results of the deliberation to the individual filing the objection.

3. Process for the review of an objection

- (1) Upon receiving a claim for reconsideration, the Director General must promptly establish a committee for the review of the objection (hereafter called the "review committee"). The review committee will consist of several JSGE members and one or more members from outside JSGE, all of whom are appointed by the Director General. The committee members will elect the chair of the review committee from among themselves. The members of the Committee on Conflict of Interest may not concurrently serve on the review committee. The review committee will hold its meeting to deliberate on the objection within 30 days of receipt of the written claim for reconsideration.
- (2) The review committee may, where necessary, listen to the opinions of the Chairperson of the Ethics Committee related to the claim and of the individual filing the objection.
- (3) Except where special circumstances exist, the review committee will prepare its report on the review of the objection and submit it to the Director General within a month of the first committee meeting held for deliberation.
- (4) The decision of the review committee will be final.

XI. Accountability to society

If disclosure of COI information of a JSGE officer or JSGE member is necessary for JSGE to fulfill its social and moral accountability, the Director General will, after deliberation by the Board of

Directors, disclose or make public, to the extent necessary, such information within and outside of JSGE to fulfill JSGE's responsibility and accountability to society. The individual to whom the COI information pertains will be given opportunity to express opinions to the Board of Directors or the director entrusted with the decision, except where the urgency of disclosing the information or making the information public precludes the possibility of listening to the opinions of the individual concerned.

XII. Education and training on research and publication ethics

The Director General must ensure that JSGE members, members of the Editorial Board, Ethics Committee, and Committee on Conflict of Interest, and members participating in development of medical guidelines have opportunities to receive continuing education and training on bioethics, research ethics, COI management, publication ethics, and related laws and ordinances. The Director General will do so by requiring completion of ethics education and training courses as a prerequisite for members to obtain or renew specialist certification.

XIII. Cooperation with related scientific societies

JSGE will work closely with many related academic societies in the fields of internal medicine and surgery, and hold consultations with them to exchange information on the revision of the Policy and on the Detailed Regulations.

XIV. Revision of the Policy

The Policy is subject to regular reviews and revisions, in consideration of the trends at the Japanese Association of Medical Sciences, to accommodate various social factors, guidelines on academic-industry partnership, revision or establishment of laws and regulations, and various requirements in relation to healthcare and research.

XV. Date of enforcement

The Policy will take effect on a trial basis for a period of two years starting on January 1, 2011, and will enter into full force and effect on January 1, 2013.

Revisions

- December 21, 2012: Change of status to a general incorporate foundation, Article II: Persons covered by the Policy, and Article VI: Method of conduct, effective as of January 4, 2013
- September 6, 2013: "clinical research" amended to "medical research," other related changes, and Article IV: Matters for disclosure, effective as of January 1, 2014
- September 8, 2015: revision, effective as of January 1, 2016

The Policy was revised on December 22, 2016. The revised Policy will take effect as of January 1,

2017.

The Policy was partially revised on September 12, 2017. The revised Policy will take effect as of January 1, 2018.

The Policy was partially revised on December 27, 2017. The revised Policy will take effect as of January 1, 2018.

The Policy was partially revised on September 6, 2018. The revised Policy will take effect as of January 1, 2019.

The Policy was partially revised on March 6, 2020. The revised Policy will take effect as of April 1, 2020.

The Guidelines Editorial Committees for the ten diseases shown below are managed under the old Policy, and as such, the above partial revision will not be applicable to those committees. (Excluded: functional dyspepsia (FD), irritable bowel syndrome (IBS), colorectal polyp, NAFLD/NASH, gastroesophageal reflux disease (GERD), peptic ulcer, inflammatory bowel disease (IBD), liver cirrhosis, cholelithiasis, and chronic pancreatitis).

The Policy was partially revised on October 5, 2020. The revised Policy will take effect as of January 1, 2021.

Appendix 1. Definitions

In preparing the definitions of terms related to medical research, reference was made to the Japanese translation, by Japan Medical Association, of the Declaration of Helsinki and to the Ministry of Health, Labour and Welfare's Ethical Guidelines for Medical and Health Research Involving Human Subjects. Efforts were also made to ensure compatibility between these documents and the contents of the Policy as much as possible.

1. Medical research involving human subjects

Activity involving human subjects (including specimens and information acquired from them) carried out for the purpose of obtaining knowledge contributing to maintain and promote national health and improving the prognosis and quality of life of patients, through identification of causes of diseases (including the frequency and distribution of various health-related incidents and factors affecting them), understanding of pathological conditions, prevention of diseases, and verification and improvement of the effectiveness of diagnostic and therapeutic methods in healthcare.

2. Clinical research

Medical research listed below that is conducted for the purpose of improving methods of prevention, diagnosis, and treatment of diseases in healthcare, of understanding the causes of diseases and their pathology, and of improving the quality of life of patients, and is subject to ethical screening.

(1) Clinical research that involves interventions and that is related to the use of drugs or medical equipment or devices in preventive, diagnostic, or therapeutic method

(2) Clinical research that involves interventions (other than (1) above)

(3) Clinical research using samples and the like and does not involve interventions.

Epidemiological research (scientific research to elucidate the frequency and distribution of various health-related incidents in a clearly defined human population and factors affecting them; also called observational study) is excluded.

3. Clinical trial

Research involving human subjects designed and conducted according to appropriate scientific principles for the purpose of evaluating clinical effectiveness of drugs (including vaccines and biological drugs), radiation therapies, psychotherapies, surgeries, medical equipment and devices, complementary and alternative medicine, etc. Clinical studies can be classified according to their objectives (General Considerations for Clinical Trials) as follows: (1) human pharmacology studies, (2) exploratory therapeutic studies, (3) confirmatory therapeutic studies (comparative studies to establish efficacy, randomized parallel dose response studies, clinical safety studies, studies of mortality/morbidity outcomes, large

simple trials, comparative studies), (4) studies on therapeutic use (comparative effectiveness studies, studies of mortality/morbidity outcomes, studies of additional endpoints, large simple trials, pharmacoeconomic studies)

4. Invasiveness

To cause stimulus exceeding that which research subjects may experience in their daily lives or injuries or distress to research subjects' body and/or mind by conducting a procedure for investigational purpose, such as puncture, incision, administration of drugs, irradiation, questions related to the subject's mental trauma, etc. Of various types of invasiveness, one causing minor effect on the research subjects' body and/or mind is called "minor invasiveness."

5. Intervention

A practice, conducted for investigational purposes, to control the presence of, or the level of the presence of, factors influencing various human health-related events (including activities to maintain and promote health and preventive, diagnostic, and therapeutic medication and examinations). Intervention may also include medical techniques beyond usual medical practice that are conducted for investigational purposes.

6. Research subject

Any individual on whom research is conducted (including individuals asked to be enrolled in the research) and any individual from whom existing specimen or information is obtained for use in the research.

7. Investigator, etc.

Principal investigator and other related persons engaged in the conduct of research (including collecting and providing samples or data at an organization engaging in such activities). Individuals who do not belong to research implementing entities and are engaged only in the provision of existing samples or data or individuals who have been commissioned by another to take part in a portion of the research are excluded.

8. Principal investigator

Any individual engaged in the conduct of research, such as writing the research protocol, as well as in overseeing the research at the research implementing entity he/she belongs to.

9. Research representative

Any individual who, in addition to writing the research protocol and otherwise engaging in the conduct of research as a principal investigator, oversees joint research with other entities.

10. Head of the research implementing entity

A representative of an incorporated entity, a head of an administrative organ, or an individual business owner who carries out research and on whom the final responsibility for the research rests.

11. Sponsor

Any individual, company, institution, or organization that has responsibility over the initiation and management of clinical research and over funds for the research.

12. Institutional COI

A state where an individual making the COI disclosure is a co-investigator or research collaborator with the research institute the individual is affiliated with or with the head of the affiliated research institute or division (e.g. university, hospital, faculty, center, etc.), and as a result, it can be anticipated that such relations may influence the activities that the individual is involved in.

13. Funder, funding agency

Any individual, company, an incorporate entity, institution, or organization that provides the necessary funds for conducting clinical research.

14. Serious Adverse Event

Any adverse event that (i) results in death, (ii) is life-threatening, (iii) requires hospitalization or prolongation of existing hospitalization; (iv) results in persistent or significant disability or incapacity; or (v) causes congenital anomaly.

15. Unexpected serious adverse event

Of the above-defined serious adverse events, any event that is not listed in the research protocol, the informed consent document, etc. or even if it is listed, is not listed at the specificity or severity stated therein.

16. Intervention research

Invasive clinical trial involving human subjects. Clinical trial conducted to collect data necessary for making an application for authorization of manufacture and sale of new drugs is called "*chiken*." Intervention research designed by a research to verify the clinical efficacy and safety of approved drugs is called "researcher-led clinical study."

17. Randomized controlled trial

Large-scale comparative clinical trial that enables objective assessment of therapeutic effect by eliminating arbitrary bias in the assessment.

18. Research implementing entity

Any incorporated entity, administrative organ, or individual business owner who carries out research. Those commissioned to take part in a portion of the research, such as storage of samples and data and statistical processing, are excluded.

19. Collaborative research implementing entity

A research implementing entity collaboratively conducting research in accordance with the research protocol. It includes entities collect samples and data from research subjects for the research and provide such samples and data to other research implementing entities.

20. Informed assent

Informed assent is given by a research subject who is objectively deemed incapable of giving informed consent. After such a subject is given an explanation, in language understandable

to the subject, and made to understand about research that is about to be commenced or continued, informed assent may be given by the subject to express agreement to the commencement or continuation of the research.

21. Informed consent

Consent given voluntarily by a research subject or his or her legally acceptable representative (hereafter collectively called “research subject, etc.”) with respect to whether the research may commence or continue (including handling of samples and data), having enough understanding after receiving adequate prior information with regard to the purpose and significance of the research, research methods, burdens on the research subjects, and predicted results of the research (including both risks and benefits).

22. Legally acceptable representative

Any individual expected to speak for the will and benefit of a research subject when the research subject is considered objectively unable to give informed consent. Such an individual can give informed consent to investigators, etc. on behalf of the research subject. When such a legally acceptable representative is speaking on behalf of any deceased research subject, the legally acceptable representatives for both living and deceased research subjects will collectively called “legally acceptable representatives, etc.”

23. Academic-industry collaboration

Academic-industry collaboration between a research implementing entity and any company, incorporated organization, and/or for-profit organization (hereafter collectively called the “company, etc.”) in medical research, including:

- (1) Joint research: research conducted by the research implementing entity and the company, etc., with each contributing research expenses and researchers (regardless of whether or not payment will be made for the research)
- (2) Commissioned research: Agreement-based research on therapies, drugs, equipment and devices of the company, etc.
- (3) Technology transfer: Commercialization by the company, etc. of results of research conducted by the research implementing entity, including the use of patents and other rights
- (4) Technical guidance: Technical guidance provided by researchers from the research implementing entity or research and development of the company, etc. carried out by researchers from the research implementing entity
- (5) Venture business originating in research implementing entity: Establishment of a venture business based on the results of research conducted by the research implementing entity and with the support of the research implementing entity
- (6) Donation: Research grant from the company, etc. to the research implementing entity

without any restriction on the use of the grant

- (7) Endowed chair: Chair established using donations from the company, etc. to the research implementing entity for the purpose of promoting research

24. Monitoring

Any act of overseeing the progress of research, and of determining whether a clinical trial is being conducted in compliance with the research protocol in ways that guarantee the ethical and scientific integrity of the trial, in order to ensure that the clinical trial is properly conducted. Such an act is performed by an individual appointed by the principal investigator (research representative).

25. Audit

Any examination, performed by an individual appointed by the principal investigator (research representative), to determine whether a clinical trial has been properly conducted, in order to assure the reliability of results of the clinical trial.