Guidance on Eligibility Criteria for Clinical Practice Guideline Formulation
The Japanese Association of Medical Sciences COI Committee 2023

Table of Contents

1. Background

Industrial-academic cooperation is indispensable for promoting clinical development and clinical research in disease prevention, diagnostics, and therapy.
Clinical research is the source of evidence-based medicine (EBM), as it enables validation of the efficacy and adverse events of multiple treatment options, and allows a systematic comparison of cost-effectiveness, therefore contributing greatly to the formulation and revision (hereinafter, formulation) of the Clinical Practice Guidelines (CPGs) to suggest optimal medical care and treatment for patients.

However, while the national medical expenditure in 2019 expanded to 44.4 trillion yen, and the total amount for pharmaceutical products was 10 trillion yen, close to a quarter of the total amount, the infrastructure for clinical research in Japan is extremely poor compared with other countries. Furthermore, the number of clinical epidemiologists, clinical biostatisticians, and clinical coordinators, establishment of data centers, and public funding support are insufficient. The quality, as well as the number of clinical research papers, are unsatisfactory, and it is difficult to say that CPG formulation based on optimal treatment and medical economics is being carried out adequately.

On the other hand, the interest of pharmaceutical companies is extremely high concerning how CPG formulation is related to sales promotion and the positioning of their products. Therefore, it is more likely for pharmaceutical companies to become deeply involved in clinical research and publishing, and the process of publicizing results, which form the basis for CPG formulation. In addition, researchers conducting clinical research develop strong financial ties with for-profit companies. In recent years, medical-related companies have been providing not only "endowments" to medical specialty societies, but also large sums of money in the form of "contracts" with the heads of specific research institutes or academic groups (e.g., specialty societies) selected through public solicitation, for the purpose of supporting education, research, and medical treatment. As a result, if researchers participating in CPG formulation are affiliated with those institutions or academic groups, there may be a serious situation of institutional COI. Suspicion is likely to arise in society and raise questions such as, “Can the independence of CPGs be kept?” “Can a fair judgment be made?” and “Will a certain company be unjustly favored?” For this reason, specialty societies that formulate CPGs are required to manage any related institutional COI.

It has been reported that when conducting or publishing intervention research involving companies, bias, i.e., trial bias (research unfavorable to companies is not conducted), publication bias (unfavorable results are unpublished), or reporting bias (efficacy is overrated, side effects are underrated), are likely to occur. Recently, several incidents of clinical research misconduct involving improper intervention of companies have been reported in Japan, undermining the international credibility of CPGs, and creating social problems.

CPGs are widely used by clinical medical societies, patient support organizations, payment agencies, medical specialists, clinicians, and consumers. With the rapid growth in the clinical development of pharmaceutical drugs and medical equipment, efforts to secure the quality and credibility of CPGs have raised much interest as an urgent issue both domestically and internationally, and specific rules have been formulated.
To formulate trustworthy CPGs based on EBM methods, it is necessary not only to disclose in detail and make public the conflict of interest (COI) of the relevant participants and societal organizations involved, but also to clearly state the eligibility criteria of those taking part in the CPG formulation, and establish a management system to prevent any risk of bias. In addition, to ensure the quality and credibility of CPGs, verification must be conducted through regular and appropriate reviews and revisions. To this end, the CPG Steering Committee, a standing committee of the affiliated society, upon collaboration with the COI Committee, must properly manage the COI of all participants involved in CPG formulation.

Therefore, based on the COI Management Guidelines of the Japanese Association of Medical Sciences, we have established this guidance on the eligibility criteria for individuals participating in CPG formulation. The purpose of this guidance is to provide information on the COI status of individuals and/or institutional COI status of affiliated institutions and academic organizations participating in CPG formulation in as much detail as possible in the prescribed form, to enable third parties using CPGs to easily and conveniently view the COI status to appropriately judge whether or not there is bias in the CPG content. This will help the affiliated society to ensure not only the quality but also the credibility of CPGs in the process of COI management.

2. Those subject to COI management

The president of the affiliated society will establish a CPG Steering Committee as a standing committee. To newly formulate or revise CPGs concerning diagnosis, treatment, and prevention, umbrella committees such as the CPG Formulation Committee (group for guideline formulation), Systematic Review Team, and External Evaluators (committee) will be established. All individuals (including committee members affiliated with patient groups) who participate in these committees, groups, and teams, in addition to spouses, first-degree relatives, or any persons with whom the participant shares income or property assets are subject to COI disclosure.

On the other hand, following the Intractable Diseases Act of 2014, the Ministry of Health, Labour and Welfare (MHLW) has been intensively promoting research on rare diseases as part of the Intractable Diseases Policy Research Project and has published several guidelines for patients and families struggling with the diseases. Members of the Japan Medical Association who participate in the formulation of such guidelines are required to disclose their COI status in the form prescribed by this guidance.

3. COI disclosure items and self-reported disclosure of COI of participating individuals and spouses, first-degree relatives, or any persons with whom the participant shares income or property assets

Participants who are engaged in CPG formulation are required to disclose the COI status for the following items using the self-reported COI form for CPG formulation participants (Fig. 1-A) for the past 3-year period starting from the previous year, for each year (from January 1 to December 31) from when the individual takes office and CPG is announced.

1) Self-reported COI disclosure of participating individuals

(1) Position as an officer or advisor of a company or for-profit organization, and amount of remuneration.
(2) Stock ownership and profit from stock (profit from stock for the previous year)
(3) Remuneration received for patent royalties or licensing fees from companies or for-profit organizations.
(4) Honoraria such as lecture fees, attending conferences (presentations, providing advice, etc.) received from a single company or for-profit organization.

(5) Manuscript fees received for writing articles, pamphlets, roundtable discussion articles, etc. from a single company or for-profit organization
(6) Research funds (joint research, commissioned research, clinical trials, etc.) provided by a single company or for-profit organization
(7) Scholarship (incentive) donations provided by a single company or for-profit organization
(8) Endowed departments established through donations by a company
(9) Other remuneration (travel expenses, gifts, etc. not directly related to research)
The amount reported in (6) and (7) is the amount actually allocated by the head of the research institution to which the researcher belongs and should be expenses and donations that can be substantially determined by the researcher.

2) COI disclosure by the spouse or first-degree relative, or any persons with whom the participant shares income or property assets
(1) Executive or advisory positions in a company or for-profit organization, and the amount of remuneration.
(2) Stock ownership and profit from stock (profit from stock for the previous year)
(3) Remuneration received for patent royalties or licensing fees from companies or for-profit organizations.

Fig. 1-A. Base amount and monetary amount category of self-reported COI disclosure items for CPG formulation participants and first-degree relatives

3) Disclosure of institutional COI regarding the participant's affiliated organization or department
Two items subject to institutional COI disclosure are education and research funds (publicly solicited or not), and scholarship (incentive) donations accepted by the head of the organization or division (research institution, hospital, department or center, etc.) with which the participant is affiliated in relation to the research content. This is applicable if the participant disclosing the COI is currently or was a collaborator or joint researcher with the head of the research institution or department for the current or past 3 years (Figure 1-B).

Fig. 1-B. Base amount and monetary amount category of institutional COI disclosure items for affiliated organizations related to CPG formulation participants.

4. COI disclosure items and monetary amount category

Participants involved in CPG formulation will disclose COI using the form prescribed, by entering the corresponding number for the item category (Form 1).

5. Basic concept of eligibility for CPG participation

The basic concept in determining eligibility for CPG participation is that if the COI status of the candidate for CPG formulation is found to exceed a socially acceptable range, or if, after CPG formulation, there is a possibility of a large financial benefit for third-party institutions and organizations from recommending the CPG for the CPG participant, spouses, first-degree relatives, or any persons sharing income or property assets either directly or indirectly with the participant, then in principle, the candidate should not be allowed to participate in CPG formulation.

1) In principle, if any of the following categories apply to the candidate for CPG formulation, or his/her spouse, first-degree relative, or any persons with whom the participant shares income or property assets, the candidate should not be allowed to participate.

(1) Income as an executive or advisor of a company or for-profit organization (500,000 yen or more /company /year)
(2) Profit from shareholding and profit income from stock (5% or more of all shares /company, or 1 million yen or more/company/year)
(3) Remuneration received for patent royalties or licensing fees from a company or for-profit organization (1 million yen or more/company/year)
(4) Affiliation with endowed departments provided through donations from a company or for-profit organization

Participants taking part in CPG revision work, and their spouses, first-degree relatives, and any persons with whom the participant shares income or property assets must avoid the above-mentioned conditions while participating in the formulation task.

2) Evaluation and management of eligibility for participants in CPG formulation according to the monetary amount category

The following illustrates the procedure for the CPG Supervisory Committee to manage the COI of participants in the CPG Formulation Committee and Systematic Review Team (Fig. 2). Eligibility for participation is determined according to the base and range of amount category items disclosed based on self-reported COI disclosure for the past 3

years (Table 1). In principle, eligibility is given to those who have items to disclose in monetary amount category②, and those who have items to disclose in monetary amount category③, should not be allowed to participate in work related to CPG formulation.

(2) Criteria and management of eligibility for participation in CPG development by monetary amount category

Table 1. Eligibility criteria and base amount per item for those participating in the CPG Supervisory Committee, CPG Formulation Committee, and Systematic Review Team

Specifically,

(1) Eligibility for participation as Head of the CPG Formulation Committee is based on self-reported COI disclosure and disclosure of institutional COI. If none of the items apply to monetary amount categories②, ③ it is possible to participate as the Head of the CPG Formulation Committee and have voting privileges. However, taking into consideration the great influence the position as Head will have on the formulation of CPGs, in cases where there are multiple items disclosed in monetary amount category①from a specific company or for-profit organization as individual and/or institutional COI that could be considered to be perceived to significantly affect the promotion of its pharmaceutical drugs and medical supplies, measures such as having the Deputy Head, who has less conflicting interests, act on behalf of the Head, but without voting privileges and the Head may be given the authority to make recommendations, should be taken. This fact should be disclosed at the beginning of the CPG main text using the prescribed form (Table 3).

(2) Eligibility for participation as a Committee Member may be considered if each item in the monetary amount category②does not exceed the base amount. If this is the case, it is possible to participate in the CPG formulation with voting privileges.
*The president of the society concerned shall have participants in the CPG formulation promptly report the occurrence of any items that fall under the monetary amount category②(Head or Deputy Head) or③(Committee Member) during the formulation period, and take appropriate measures.

(3) Participants in CPG formulation shall promptly report to the head of the relevant society if an item falls under monetary amount category②(Head or Deputy Head) or ③(Committee Member) during the period of CPG formulation, who will take

appropriate action.

6. Structure of the CPG Formulation Committee

Participants for the CPG Formulation Committee will be selected as members based on eligibility criteria but the following points should be noted in the structure of the committee.

1) The number of members having items to disclose in monetary amount category② should not exceed the majority of the total number of members.
2) The committee should be structured so that diversity of the participant's area of expertise is emphasized, including epidemiologists and statisticians, and should not be biased toward members who have conflicting interests with a specific company or for-profit organization.
3) Since CPGs serve as a source of information to support the decision-making by patients and healthcare workers in the medical field, those representing patients and civic groups should be invited as members of the CPG Formulation Committee and aim for a committee that is structured so that different values can be shared.

7. Responsibilities of the Head of the CPG Formulation Committee

1) At the time of CPG publication, the head must disclose the COI status of each participant including the affiliation and title for the past 3 year-period starting from the previous year, by classifying the participants into CPG Supervisory Committee, CPG Formulation Committee, and Systematic Review Team and External Evaluators, using the prescribed form (Table 2). This information must be placed either at the beginning or end of the CPG main text and made public.

Table 2. Example of COI disclosure for participants of CPG formulation

2) However, if a situation arises that a member of the Formulation Committee has items in monetary amount category② that exceeds the base amount and are relevant to the amount in category③, if the individual is indispensable to the formulation of CPG, and if the transparency and neutrality can be ensured, participation can still be granted in the CPG formulation process.

However, the president of the affiliated society must take measures such as not having the authority in the final decision-making in CPG formulation and fulfill obligations to fulfill accountability to society by disclosing COI and the names of those who abstained from voting for each CQ number at the beginning of the CPG main text (including

updates), as shown in Table 3.

Table 3. Disclosure for abstention at CPG formulation meetings to select clinical guidelines (example)

3) In addition, the source of the funding used for CPG formulation must also be disclosed. That is, at the time of CPG publication, 1) the name of the company that provided funding (donations, etc.) for activities of the affiliated society (academic lectures, etc.), and 2) the name of the company that provided funding (includes labor) concerning the formulation of CPG, must be disclosed using the designated form (Table 3) for the past 3 year-period starting from the previous year.

The institutional COI of the affiliated society itself related to the contents of the clinical guidelines to be established (including revisions) must be disclosed in the prescribed form (Table 4). That is, at the time of CPG publication of the CPG, the names of third-party organizations and groups that have provided funds (educational or research support funds, donations, joint research funds, etc.) to the affiliated society concerned for the past 3-year period, their breakdown, and the names of the business activities covered must be described and disclosed. However, the amount paid by a company to the relevant affiliated society for an event (academic seminars, exhibition halls, etc.) co-sponsored by the company in connection with the holding of an academic meeting is not subject to disclosure.

4) When recommendations of the CPG are publicized through media, the COI status of participants in the formulation should be disclosed. In particular, the same applies to publications in company-related promotional brochures and/or commercial magazines.

5) In the case of COI disclosure, the COI status of individual participants and their research institutions and academic organizations related to the contents of the formulated CPG must be disclosed in the CPG main text in the prescribed format. However, if the volume of disclosure is large, Tables 2, 3, and 4 may be substituted by including a URL or QR code (viewable by smartphones) in the CPG text that will allow easy access to the disclosed information on the relevant society's website, instead of including them in the CPG.

8. Matters to consider when formulating CPG

To improve the quality of CPG content and ensure credibility, the head of the committee involved in CPG formulation should handle the following items appropriately.

1) Obtaining the name of the company or for-profit organization involved with the manufacturing and sales of pharmaceutical drugs or medical equipment mentioned in the CPG before CPG formulation.
2) Assessment of CPG contents with a cost-effective perspective
3) Verifying and securing the neutrality and fairness of CPG contents
4) Managing and recognizing any COI between the participant in CPG formulation (including external evaluators), spouses, first-degree relatives, or any persons with whom the participant shares income, and the company or for-profit organization involved.
5) The sharing of COI information of each participant by all those participating in the CPG Formulation Committee.
6) Acceptance and appropriate handling of comments received from other related institutions and organizations of which a COI exists
7) Acceptance of an external evaluation to improve the credibility of CPG
8) Disclosure of funding sources related to expenses required for CPG formulation and publication
9) Disclosing the contents of any financial support from a company etc. involved in the contents formulated, to the related organization
10) Acceptance of advice etc. for CPG formulation (revisions) based on evaluation results of a third-party organization (e.g. Japan Council for Quality Health Care, Medical Information Network Distribution Service (Minds))
11) Establishing disciplinary rules and regulations for violators of the guidelines

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