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Letter to the Editor

Evaluation of financial conflicts of interest and drug statements in the coronavirus disease 2019 clinical practice guideline in Japan

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To the editor

Since the coronavirus disease 2019 (COVID-19) outbreak in late 2019, evidence on its treatment has accumulated rapidly. Accordingly, many countries subsequently drafted COVID-specific clinical practice guidelines (CPGs). While CPGs allow healthcare professionals to standardize and improve patient care, inappropriate biases may arise when the authors have financial conflicts of interest (FCOIs) directly related to those recommendations. In Japan, the Ministry of Health, Labour and Welfare (the Ministry) funded the COVID-19 CPG development. Originally published in March 2020, the COVID-19 CPG has undergone multiple revisions. The most recent of these, the fifth edition, was published on 26th May 2021. Consequently, we considered this latest version for this study [1].

We examined all COVID-19 CPG fifth-edition authors and their financial relationships with pharmaceutical companies between 2017 and 2019. These data were voluntarily published by all 79 pharmaceutical companies belonging to the Japanese Pharmaceutical Manufacturers’ Association. However, this Association does not impose penalties for non-compliance with the guidelines mandating payment disclosure.

First, we descriptively analysed the authors’ demographic characteristics and financial relationships with the pharmaceutical companies manufacturing the drugs listed in the COVID-19 CPG. We also assessed the CPG management policy on FCOIs. We then reviewed the statements of the COVID-19 drugs listed in the CPG and the evidence cited to support them. Details of the methodology are summarized in the Supplementary Material 1.

The 23 COVID-19 CPG authors were all male and content experts. For further details, refer to Supplementary Material 2.

Twenty (87.0%) of these authors received at least one payment from a pharmaceutical company. In all, 50 companies (63.3%) made combined payments totalling $2,823,477, of which $1,915,196 (67.8%) consisted of scholarship donations, and another $908,281 (32.2%) were personal payments (Table 1). The combined 3-year average total payment per author was $122,760 (standard deviation (SD) $233,538). Additionally, payments from three of the manufacturers of the COVID-19 drugs included in the CPG (Supplementary Material Table S3) accounted for 8.4% of the total payments ($236,294). Of these, Chugai Pharmaceutical Company (the distributor of tocilizumab in Japan) contributed the most at $153,368, while FUJIFILM Toyama Chemical Company (the manufacturer of favipiravir) paid the least at $32,574 (Table 1). Nine authors (39.1%) received at least one payment from these three companies. Since there were no COI statements in the CPG, we contacted the Ministry about its management of CPG author-related FCOIs. Despite four such attempts between June and August, we have received no formal response as of 15th October 2021.

Supplementary Material 3 provides summaries for the drugs recommended in the COVID-19 CPG. As of June 2021, of the five drugs listed in the CPG, remdesivir, dexamethasone, and baricitinib...
received approval for COVID-19 patient treatment in Japan. The other two, tocilizumab and favipiravir, have not. Interestingly, while tocilizumab received a mixture of positive and neutral findings for COVID-19 treatment, the CPG discouraged its use. In contrast, favipiravir received a positive assessment with the embedded description inviting participants in a Ministry-sponsored observational study.

Overall, our study found significant FCOIs between the government COVID-19 CPG authors and pharmaceutical companies. We further note poor management of these FCOIs by the Ministry. The average personal payments of 2017 to 2019 were disclosed on those companies’ websites. Japanese yen (¥) was converted to U.S. dollars ($) using the 2017 average exchange rate of ¥112.1 per $1, 2018 average exchange rate of ¥110.4 per $1, and ¥112.1 per $1, 2019 average exchange rate of ¥109.0 per $1. Abbreviation: COVID-19, coronavirus disease 2019.

We evaluated the personal payments, including lecturing, consulting, and writing reimbursements, and scholarship donations from pharmaceutical companies using the payment data from 2017 to 2019, which were disclosed on those companies’ websites. Scholarship donations represent funds provided to medical institutions and various departments to encourage educational and academic activities related to the development of new drugs. Japanese yen (¥) were converted to U.S. dollars ($) using the 2017 average monthly exchange rate of ¥112.1 per $1, 2018 average exchange rate of ¥110.4 per $1, and ¥112.1 per $1, 2019 average exchange rate of ¥109.0 per $1. Abbreviation: COVID-19, coronavirus disease 2019.

We propose that the Ministry ensures a more transparent and rigorous approach to CPG development. This should include a more balanced author selection process, full COI disclosure, systematic evidence quality assessment, and appropriate recommendations based on established CPG development methodology.

**Author contributions**

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AM, AO and TT: study supervision. TH and AM: statistical analysis. All authors: study concept and design, acquisition, data analysis. AM, AO and TT: study supervision. TH and AM: statistical analysis. All authors: study concept and design, acquisition, analysis, or interpretation of data, and drafting of the manuscript.

**Transparency declaration**

As non-financial conflicts of interest, Anju Murayama, Akihiko Ozaki, and Tetsuya Tanimoto have several research articles related to the conflicts of interest among healthcare professionals in Japan. Drs Ozaki and Tanimoto received personal fees from Medical Network Systems outside the scope of the submitted work. Dr Tanimoto also received personal fees from Bionics Co. Ltd, outside the scope of the submitted work. This study was funded in part by the Medical...
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.11.019.

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