Editorial
What has happened since the implementation of the Clinical Trials Act?: epidemiologists need to know

Yuri Ito¹, Seiichiro Yamamoto²,³, Kenichi Nakamura⁴

¹ Osaka Medical and Pharmaceutical University, Osaka, Japan
² Shizuoka Graduate University of Public Health, Shizuoka, Japan
³ National Cancer Center Institute for Cancer Control, Tokyo, Japan
⁴ National Cancer Center Hospital, Tokyo, Japan

Corresponding author:
Yuri Ito, PhD
Associate Professor
Department of Medical Statistics, Research & Development Center
Osaka Medical and Pharmaceutical University
2-7 Daigaku-machi, Takatsuki City Osaka, 569-8686, Japan
TEL: +81-72-683-1221 (ext. 3954) +81-72-684-7255 (Direct)
E-mail: yuri.ito@ompu.ac.jp

Short title: The impact of the Clinical Trials Act

1016 words
8 references

Tables: 0
Figures: 0
Tsutsumi et al. have reported a decrease in the number of clinical trials in Japan following implementation of the Clinical Trials Act (CTA) in 2018. The CTA was introduced to improve the quality and transparency of clinical trials in Japan. However, the installation of the new Act, especially administrative processes such as verification of conflict of interests, submission of the trial plan to the government, and increased review fees for review board certification were extremely burdensome. As a result, some research activities in Japan may have been suppressed.

Tsutsumi et al. collected data on clinical studies using UMIN-CTR and analysed 16,455 studies which started between April 2015 and March 2019. The dataset included clinical studies started one year after implementation of the CTA (April 2018 to March 2019). They analysed trends in the number of clinical trials per month using interrupted time series analysis (ITSA). They observed a significantly decreasing trend in the course of one year following the CTA implementation. In particular, studies with smaller sample sizes (<100), interventional designs, and non-profit funding sponsors decreased considerably. Although it is very important to improve quality and transparency of clinical studies in Japan, there is a serious problem if research activities in Japan have been suppressed by the new legislation. This high impact result showed the need for support of clinical studies in Japan.

Although the authors did not suggest this in the article, the decreasing trend of new clinical studies after the CTA implementation might be strongly related to the increased workload for the reauthorization of studies which had started before the Act, as a transitional measure of the CTA. Research institutes with a larger number of studies might have faced an onerous and time-consuming task in completing reauthorization for the certification review board (CRB).

According to a survey of the Japanese Cancer Trial Network (JCTN), which is a consortium of large clinical trial groups in Japan, the number of clinical trials JCTN conducted increased after FY2019, although the number had decreased once in FY2018, just after the CTA implementation. The research facilities in the JCTN have adapted to the CTA after one year but with a significant cost, especially in terms of increased expenditure, staff costs and difficulties of complicated administration for the support section and researchers. According to a survey by Kunito et. al, about 80% of researchers reported that burden of the CTA implementation includes an increase in the cost of the CRB and insurance for clinical trials, and complicated administrative processes including
setup for new research and small changes to protocols. In addition, over 80% complained about the discrepancy in interpretation of the usage and dosage of medication between the clinical and the research setting under the CTA.4

Research institutions and hospitals in the JCTN might have quickly adapted to the CTA one year after implementation. However, many researchers and institutions with insufficient supporting resources might still have struggled with burden of cost and complicated administration. We need to consider the problem in order to improve the situation and boost clinical research activities in Japan. For example, leading groups such as the JCTN have accumulated tips on how to deal with the CTA and started to share effective strategies with other research institutions.5,6 As Tsutsumi et al. also suggested, further middle- or long-term monitoring is needed after 2020 using public data from UMIN-CTR and jRCT. In addition, we need to be conscious of inequalities in research environment among research institutions regarding financial and human resources.

Revision of the CTA is also proposed by several research associations, such as JCTN7, The Japanese Medical Science Federation8 and Japan Society of Clinical Trials and Research, which support clinical studies in academic settings in order to reduce complicated processes with reliability and transparency of clinical studies.7 Revision of the Act is required to clarify some points, e.g. to show a clear distinction between the clinical research covered by the CTA and the Ethical Guidelines for other interventional and observational research. Ideally, if the intervention trials were conducted following the CTA rules, evidence from trials of sufficient quality could be used for the process of authorization and/or indication expansion of drugs. Amendment of the CTA is now under discussion in the committee of the Ministry of Health, Labour and Welfare. The CTA is to be amended within 5 years of implementation; reasonable revisions are expected to be made to revitalize the clinical trial activity, keeping the trial quality and subject safety sound.

Another issue of the CTA is the lack of international consistency. When international clinical trials are conducted under the CTA, Japanese investigators necessarily confront several difficulties to harmonize the CTA with the regulation policies of other countries. For example, the unclear scope of the CTA, absence of the concept of sponsorship, extreme regulation regarding the development of medical devices, the unique rule of serious adverse event reporting, and overly strict COI management differ from international standards. In light of the COVID-19 situation, we should not just push forward considering Japan in isolation, but should take it in the direction of international
consistency and international joint development of new medicines and devices.

Implication for epidemiologists
In Japan, there are still small number of interventional trials in the field of epidemiology, and the use of observational studies is widespread. Although it is very important to reveal the relationship between exposure and outcome using observational data, we can move on to the next step of developing preventive strategies and effective behavioural changes using the interventional study approach after the identification of risk factors. In addition, a sizeable number of members often support clinical studies as an epidemiologist or biostatistician. Therefore, epidemiologists need to know the basic methods and rules of interventional studies. We also need to be aware of the influence of the implementation of the CTA, and the issues and points that need to be revised. We hope that our epidemiologists can understand the situation and boost the possibility of conducting more interventional studies in the field of epidemiology in Japan.

Disclosure
YI received honoraria for a lecture from KYORIN pharmaceutical CO., Ltd. SY received honoraria for a lecture from Janssen. KN received honoraria for lectures from Chugai Pharma, Bayer Yakuhin, and Taiho Pharmaceutical.

References
1. Tsutsumi I, Tsutsumi Y, Yoshida C, Komeno T, Imanaka Y. Impact of the Clinical Trials Act on noncommercial clinical research in Japan: An interrupted time-series analysis. Journal of Epidemiology. in press.
2. Nakamura K, Shibata T. Regulatory changes after the enforcement of the new Clinical Trials Act in Japan. Jpn J Clin Oncol. 2020;50:399-404.
3. Nakamura K. Response and challenges to the Clinical Trial Act in the research supporting field. Web symposium of the Society for Regulatory Science of Medical Products. 2021.
4. Kunito E, Ariyoshi K, Inoue A, Tsuboi M. A Survey of Researchers on Clinical Trial Act. Jpn Pharmacol Ther. 2019:S59-S66.
5. Japan Clinical Oncology Group. Protocol Manual. [cited 2021 4 Oct]. Available from: http://www.jcog.jp/doctor/tool/manual.html
6. Introduction to Clinical Research website [homepage on the Internet] [cited 2021 4 Oct]. Available from: https://www.icrweb.jp/icr_index.php
7. Japanese Cancer Trial Network, Proposal for the revision of the Clinical Trials
Act. [cited 2021 4 Oct]. Available from: http://jctn.jp/doc/JCTN_20190819.pdf

The Japanese Medical Science Federation, Proposal for the revision of the Clinical Trials Act. [cited 2021 4 Oct]. Available from: https://www.rinspo.jp/files/publicity_190708.pdf